CYCLAZINES AND RELATED N-BRIDGED ANNULENES

by

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For my family, with thanks
for support and encouragement.

DECLARATION

I declare that this thesis is my own composition and that the work described within has been carried out by myself and has not been submitted previously for any Higher Degree. This thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. D. Leaver between October 1986 and September 1989.

The following lecture courses were attended during the three years of research:

"Mass Spectrometry"

Professor K.R. Jennings (University of Warwick).

"Cell Biology"

Dr. Phillips (University of Edinburgh).

"Catalysis and the Chemical Industry"

Employees of I.C.I. (Grangemouth).

"Medicinal Chemistry"

Professor P.G. Sammes (Smith Kline and French).

"Introduction to Management"

Department of Business Studies (University of Edinburgh).

"Recent Advances in Organic Chemistry (I)"

Department of Chemistry (University of Edinburgh).

"Industrial Processes"

Employees of I.C.I. (Grangemouth) and Department of Engineering (University of Edinburgh).

"Recent Advances in Organic Chemistry (II)"

Department of Chemistry (University of Edinburgh).

Attendance at the R.S.C., S.C.I. 5th Medicinal Chemistry Symposium (Cambridge University, September 1989).

Attendance at the departmental seminars and colloquia over the three years.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Dr. Derek Leaver for suggesting the topic of research described in this thesis, for his continual guidance and support throughout the three years, and for his unfailing inventiveness and enthusiasm for the work undertaken.

I would like to thank the University of Edinburgh for the provision of laboratory facilities and technical services and the S.E.R.C. for a research studentship.

Finally, I would like to thank Mrs. Lynn Marouf for her skilful and efficient typing of this thesis and Mr. D. Smith for the provision of binding facilities.

CONTENTS

ABSTRACT

This thesis documents the investigation of synthetic routes to 1,3-diaza[3.3.3]cyclazine, the only diaza-[3.3.3]cyclazine as yet unsynthesised, and to a related doubly N-bridged [18]-annulene, namely pyrazino[2,1,6-*de*:5,4,3-*d'e'*]diquinolizine.

Activation of the 6-position of quinolizine-4-thione was achieved by means of cyclopalladation. Modification of the cyclopalladated ligand followed by thiode-palladation using morpholine-N-sulphenyl chloride afforded [1,2,4]-dithazolo[3,4,5-*de*]quinolizinium perchlorate. A number of attempts to convert this to the 1,3-diaza-[3.3.3]cyclazine are described and spectroscopic data of the target compound are discussed and compared with other members of the series.

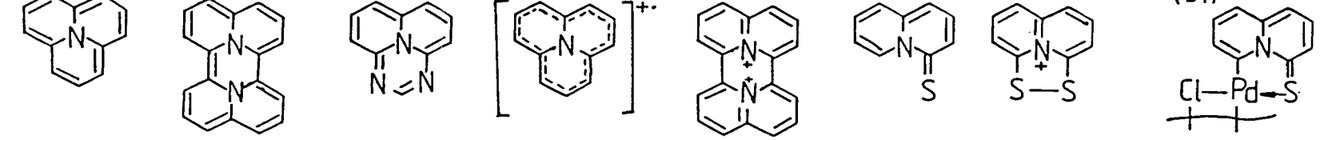
Reactions of [1,2,4]-dithiazolo[3,4,5-*de*]quinolizinium perchlorate with a variety of nucleophiles, including active methylenes are investigated. Treatment of this dithiazolium salt with divalent palladium and nickel ions in the presence of sodium borohydride is reported to give interesting dimeric metal complexes. The nickel complex thus obtained underwent a thermally-induced sulphur extrusion reaction to yield the novel doubly cyclonickelated complex bis(4-thioquinolizin-6-yl-S)-nickel(II)). Attempts to cause reductive coupling of the quinolizine-4-thione ligands of this complex with cobalt

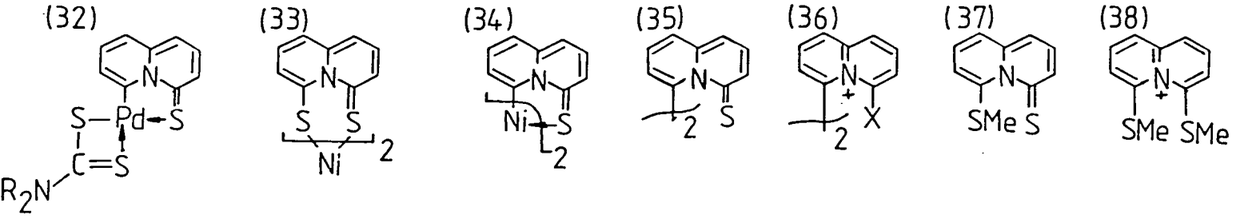
tris(trifluoroacetate) are briefly described.

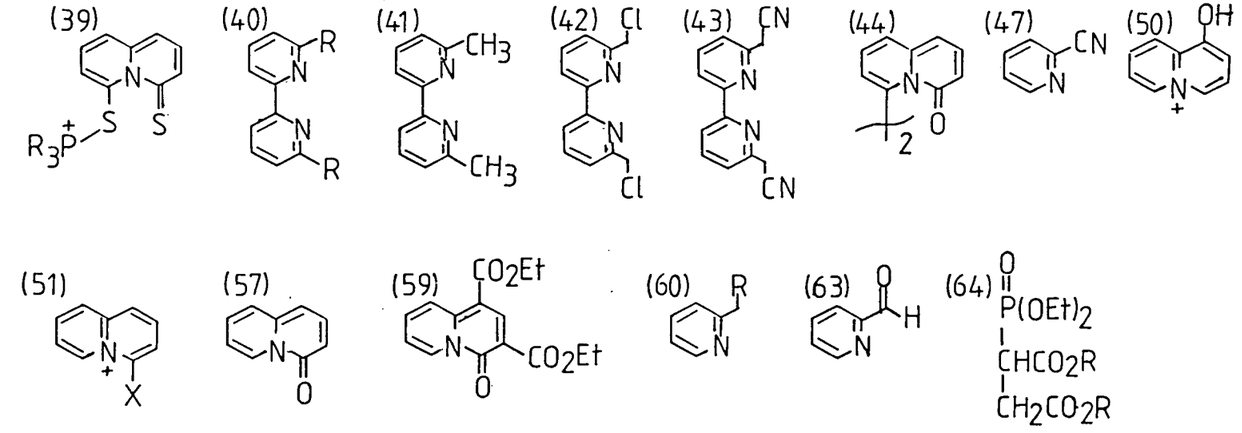
An alternative approach to the [18]-annulene system *via* symmetrical 6,6'-disubstituted-2,2'-bipyridines is reported. Suitably substituted 2-pyridines are used as models and modification of these substituents to form quinolizin-4-ones, 1-hydroxyquinolizinium ions and 4-halogenoquinolizinium ions is investigated. The results of the model systems are applied to the bipyridine series and attempts to form 6,6'-bis(quinolizin-4-ones) are described. A number of cyclisation procedures are investigated.

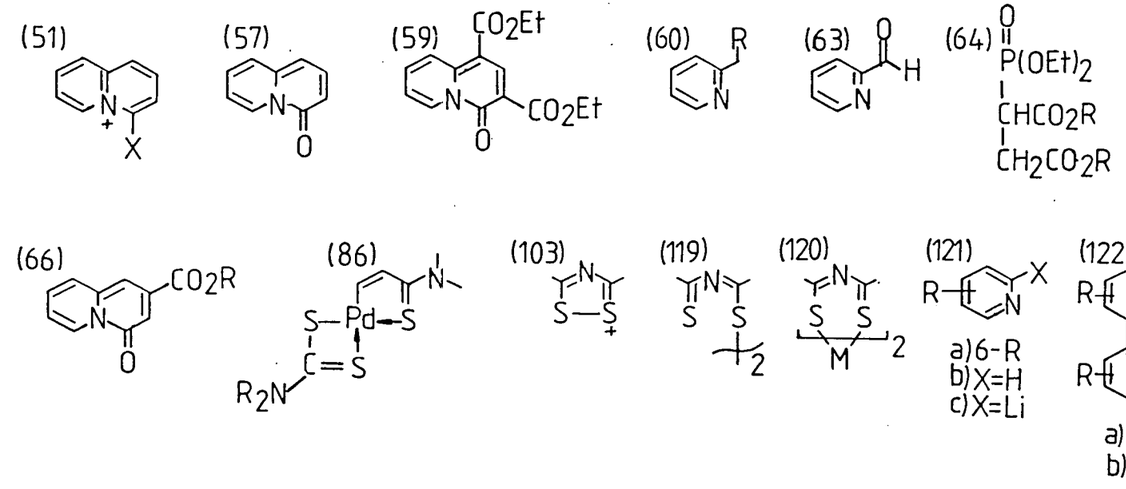
The synthesis and oxidation reactions of some quinolizine-4-thiones with metal oxides is reported. A novel isomerisation was observed in the presence of copper oxide and a mechanism for this isomerisation is proposed.

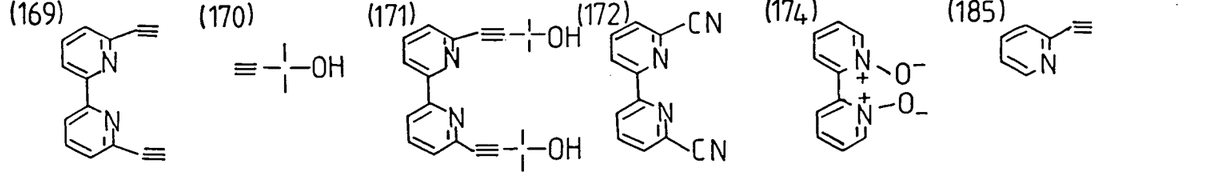
INTRODUCTION

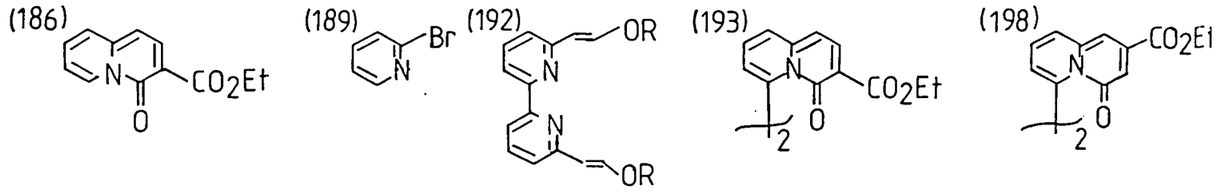


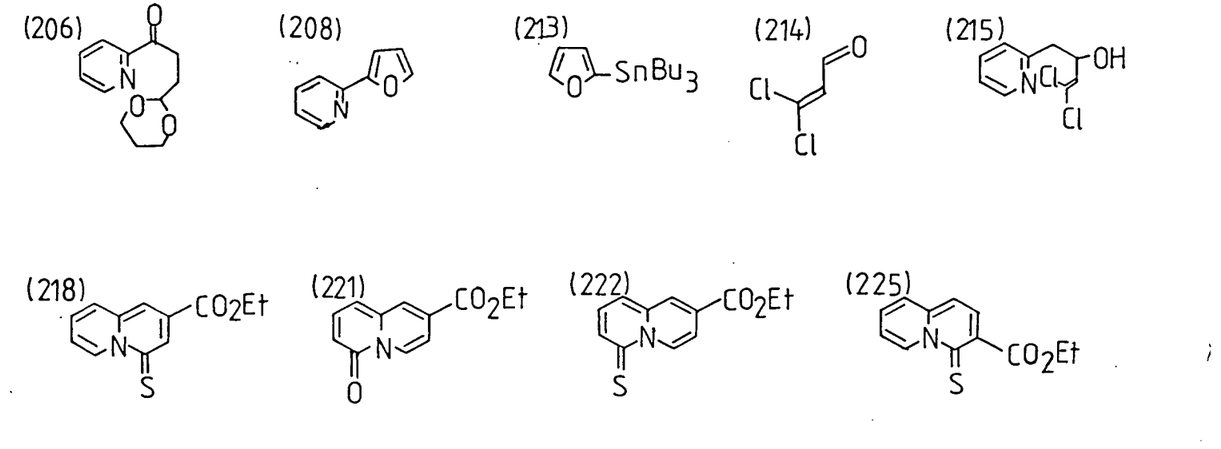


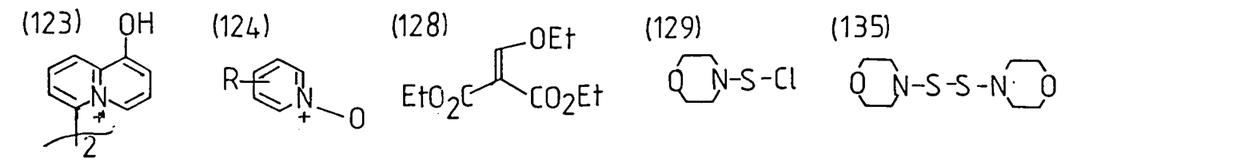


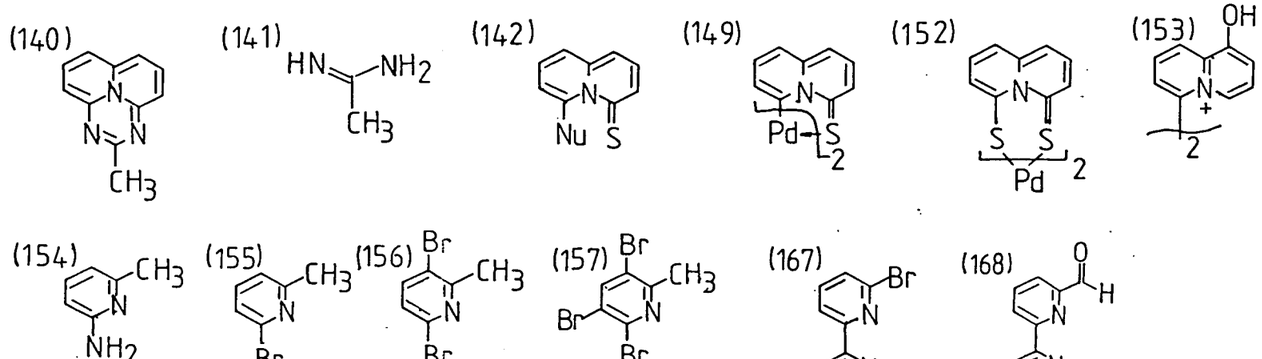


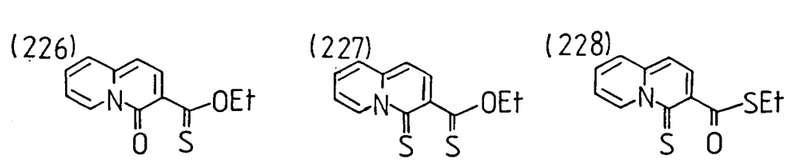


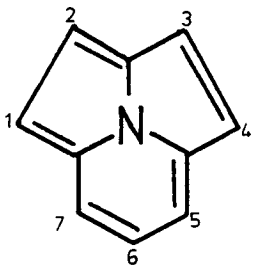












[2.2.3] CYCLAZINE
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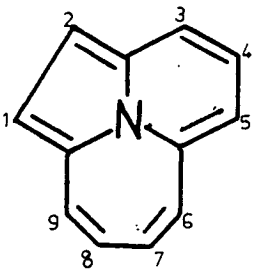
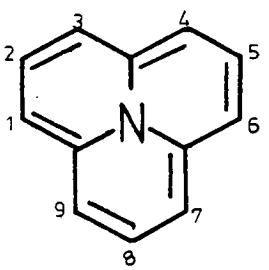
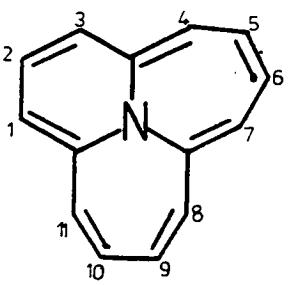


[2.3.4] CYCLAZINE
(2)



[3.3.3] CYCLAZINE
(3)



[3.4.4] CYCLAZINE
(4)

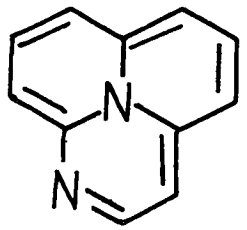
CYCLAZINES

The term "cyclazine" was originally proposed by Boekelheide[1] to describe "the general case of a conjugated, unsaturated cycle held planar by three covalent bonds to an internal nitrogen atom". Such compounds are derivable from annulenes by replacement of three inwardly-directed hydrogen atoms by a central nitrogen atom, making them nitrogen-bridged annulenes.

The original system of nomenclature[1] was modified by Leaver[2] and distinguishes individual members by specifying the number of atoms in the annulene ring that lie between the points of attachment to the central nitrogen. These three numerals are placed in front of the word cyclazine and listed in increasing order so that their sequence starts at the same point and proceeds in the same direction as the I.U.P.A.C. numbering sequence of the peripheral annulene ring. Structures (1) to (4) exemplify this modified nomenclature.

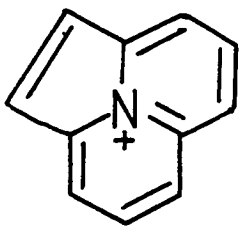
The systematic fusion nomenclature for these compounds, based on I.U.P.A.C. rules[3], is derived from the largest named nitrogen-containing ring system present in the molecule. Thus (1) becomes pyrrolo[2,1,5-*cd*]-indolizine and (3) becomes pyrido[2,1,6-*de*]quinolizine.

Substitution of a peripheral sp^2 carbon atom by a heteroatom may be indicated by using the "replacement nomenclature" system. Thus (5) becomes 1-aza[3.3.3]-cyclazine.



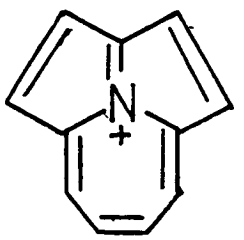
(5)

The cyclazine system of nomenclature has been further extended to accommodate ionic systems as shown for formulae (6) and (7). However, the following brief description is limited to neutral molecules.



[2.3.3]CYCLAZINIUM ION

(6)



[2.2.4]CYCLAZINIUM ION

(7)

[2.2.3]Cyclazine (1) is a [4n+2]-annulene system with 10π electrons. Compounds in this family are stable, aromatic and have been extensively investigated. The

parent compound was originally synthesised by Boekelheide and co-workers[4] in 1959. Since then many derivatives and aza-analogues have been synthesised[5], among them 1-aza-, 2-aza-, 5-aza-, 6-aza- and 1,4-diaza-[2.2.3]cyclazine. In terms of reactivity, the parent of the family shows the normal behaviour of a stable aromatic system, undergoing electrophilic substitution reactions at the 1- and 4-positions smoothly and in good yields[4].

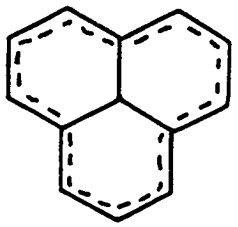
[2.3.4]Cyclazine (2), known only as its 4,5-di(alkoxycarbonyl)-derivatives, is a [4n]-annulene system with 12π electrons. According to their proton n.m.r. spectra, these compounds are paratropic and they readily undergo addition reactions (hydrogenation, Diels-Alder) to the diene system in the seven-membered ring.

Of greater relevance to the present work is [3.3.3]-cyclazine (3) which, like (2), is a [4n]-annulene system with a 12π periphery. The parent of the series was first synthesised by Leaver and co-workers[6] after considerable effort by a number of other groups. The difficulty arose from the unexpectedly high reactivity of the compound and the successful synthesis took advantage of incorporating stabilizing substituents in active positions, which were removed in the final step.

The high reactivity of [3.3.3]cyclazine can be rationalised by considering its frontier molecular orbitals. In this respect, qualitative comparison with

Fig (1)

the phenalenyl ring system (8) is useful. The π-system of (8) has a non-bonding molecular orbital (N.B.M.O.) (9) which may be doubly-, singly-, or un-occupied, giving rise to an anion, a radical and a cation, all of which exhibit considerable stability. Replacement of the central carbon atom by nitrogen leads to the parent [3.3.3]cyclazine (3), its radical-cation and its dication respectively. The latter two have been obtained by sequential oxidation of the parent with chlorine or bromine[6].



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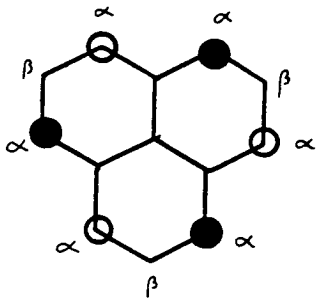


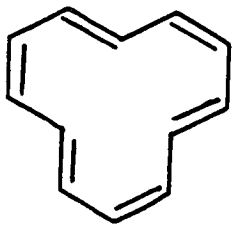
(9)

Comparison of the proton n.m.r. spectra of the diamagnetic members of the above series gives rise to some interesting results, Fig. (1).

Structure (9) indicates that the orbital coefficients of the N.B.M.O. are non-zero only at the α-positions, thus the charge in the phenalenyl anion and cation is largely concentrated at these positions. The effect of this on the α-protons (doublet) relative to the β-proton (triplet) is deshielding in the cation and shielding in the anion. The same effect is seen in comparing the spectrum of the neutral cyclazine (3) with that of the dication.

The effect of replacing a carbon atom by a nitrogen is

to increase the positive charge by one unit and thus the spectrum of the cyclazine dication is shifted to a higher frequency than that of the phenalenyl cation. However, the corresponding change from phenalenyl anion to neutral [3.3.3]cyclazine exhibits a shift to lower frequency. This apparent anomaly may be explained as follows: the cyclazine would exist as a zwitterion if it were to retain the electron distribution of the phenalenyl anion; thus in order to avoid this energetically unfavourable situation, the non-bonding electrons of the cyclazine tend to localise largely in a nitrogen lone pair orbital, leaving a 12π periphery, equivalent to [12]-annulene (10) which sustains a paramagnetic ring current, resulting in extremely strongly shielded protons.

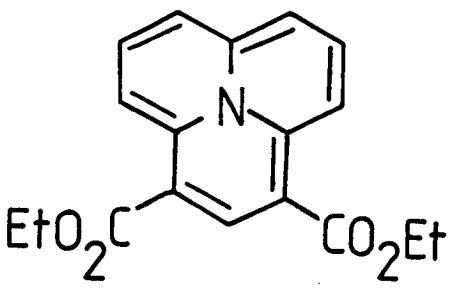


(10)

The observation of this strong paratropism indicates the existence of a low-lying excited electronic state. Indeed this correlates well with the low energy of the first electronic transition which occurs at 93 kJ mol^{-1} (ref. 7) and the susceptibility of the compound to oxidation by molecular oxygen.

[3.3.3]Cyclazines are very sensitive to inductive perturbations, as ascertained by Leupin and co-workers[7]. Thus the introduction of electron-withdrawing groups or aza-substitution at one or more α-positions has the effect of lowering the energy of the highest occupied molecular orbital, thus conferring enhanced stability on the [3.3.3]cyclazine nucleus. Numerous aza-analogues of [3.3.3]cyclazine have been synthesised[5] and are known to be less reactive than the parent.

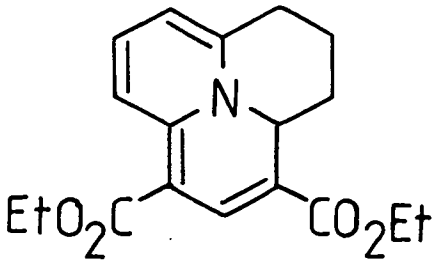
Known reactions of the parent [3.3.3]cyclazine are limited to the oxidation reactions previously mentioned. Most of the investigations of reactivity have been carried out on the inductively-stabilised 1,3-di(ethoxycarbonyl)-derivative (11).



(11)

Its reactivity is typical of the [3.3.3]cyclazine nucleus in reflecting lack of aromatic character, particularly in the ease with which addition and oxidation reactions occur. The former proceed in such a way that the adduct, e.g. the tetrahydro-derivative (12), exhibits the stable conjugation of a 4H-quinolizine substructure

bearing electron withdrawing groups at positions 1 and 3 (13).



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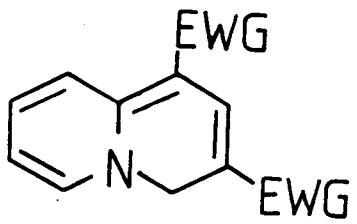
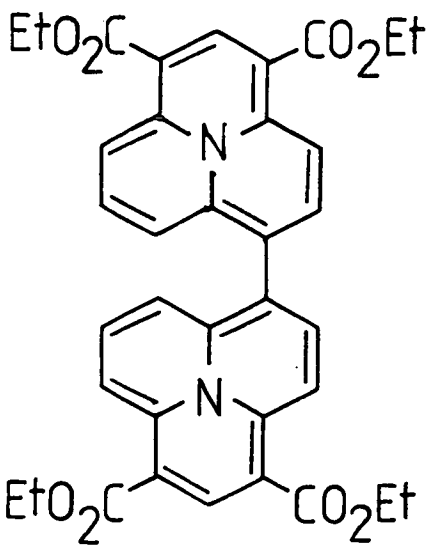


(13)

Oxidation reactions did not give stable monomeric cations analogous to those obtained with the parent, and the only isolated products were the bicyclazine (14) and/or the diazoniadibenzoperylene salt (15).



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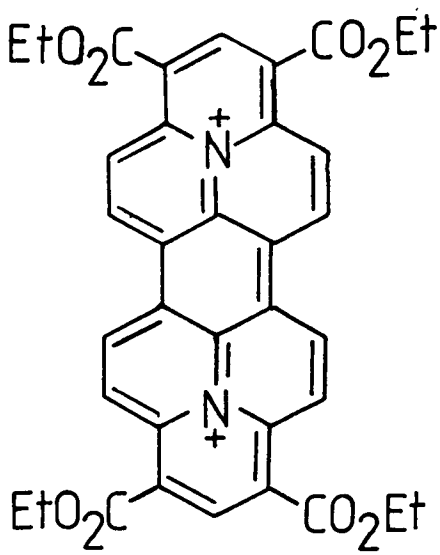

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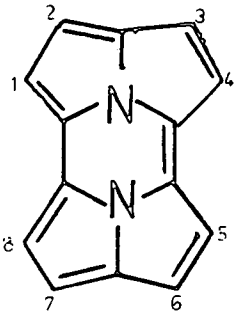
Despite the lack of aromatic character of [3.3.3]-cyclazines, their participation in electrophilic substitution reactions has been observed[6a] in cases where



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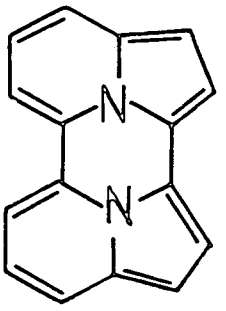

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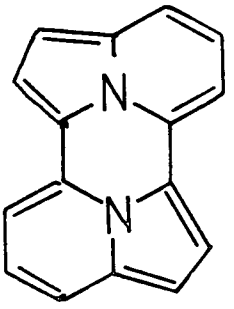

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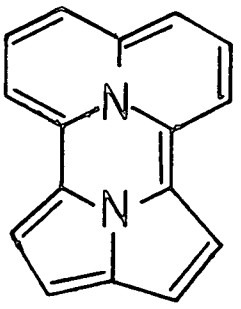

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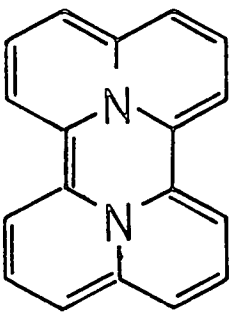


(20)

one or more electron-withdrawing substituents was present. Such reactions occurred at one or more of the remaining α-positions.

[3.4.4]Cyclazine (4) is a [4n+2]-annulene system with 14π electrons. According to P.M.O. considerations[5], however, it should be non-aromatic. It is the last remaining cyclazine included in the original proposals[4] which has not yet been synthesised. Since it does not contain a bicyclic substructure that is inherently stable, approaches to its construction are likely to be far from simple.

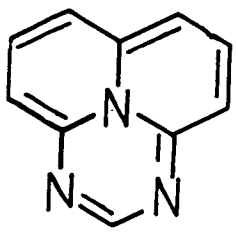
DOUBLY N-BRIDGED ANNULENES

The extension of the cyclazine concept to higher bridged annulene systems is possible, formally by joining two internal nitrogen atoms, each by three covalent bonds, to the annulene perimeter. The possible structures resulting from this replacement, restricted to molecules containing five- and six-membered rings, are shown in formulae (16)-(20).

Examples of the first[8] and third[9] molecules have been synthesised. Pyrazino[2,1,6-*cd*:5,4,3-*c'd'*]dipyrrolizine (16) is a [4n+2]-annulene system with 14π electrons and is therefore aromatic, undergoing electrophilic substitution to give 1-substituted, 1,5-disubstituted or 1,8-disubstituted products. In this respect it is similar to

its [10]-annulene relative, [2.2.3]cyclazine (1). Pyrazino[2,1,6-*cd*:5,4,3-*c'd'*]di-indolizine (18) is a [4n]-annulene system with 16π electrons and is therefore potentially antiaromatic. It does, however, possess two potentially aromatic substructures - the indolizine nuclei. Although the parent compound has not yet been prepared, n.m.r. data (^{13}C and ^{1}H) of the 1,6-dimethyl derivative suggest that there is no increase in carbon π-electron densities with respect to those of indolizine, but that the methine and methyl protons are appreciably more shielded than the corresponding indolizine protons. This shielding effect is attributed to the paratropic 4n π-electron perimeter. The chemical properties of this ring system have not yet been studied, although its instability in the presence of oxygen is readily apparent.

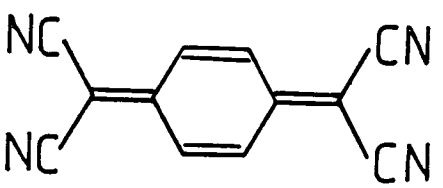
One logical objective for future work in the area of N-bridged annulenes in general would be to synthesise members of the series which are, as yet, unknown. The work described in this thesis outlines synthetic approaches to 1,3-diaza[3.3.3]cyclazine (21) and pyrazino-[2,1,6-*de*:5,4,3-*d'e'*]diquinolizine (20).



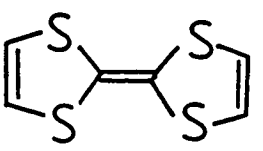
(21)

In addition to their novelty, these compounds are of interest in the field of "organic metals".

Although most organic solids are electrical insulators, several charge-transfer complexes of the planar, conjugated electron acceptor tetracyanoquinodimethane (TCNQ) (22) and suitable planar, conjugated electron donors such as tetrathiafulvalene (TTF) (23) are known to be electrically conducting. In fact the specific TTF-TCNQ example, like many of its close analogues, is an organic metal, i.e. its conductivity increases with decreasing temperature until a maximum is reached near 59K[10]. Beyond this point the salt acts as a semiconductor, so its conductivity decreases with decreasing temperature. Both TTF and TCNQ are planar, and individual molecules can approach closely in the direction perpendicular to their molecular planes to form segregated stacks with interplanar distances of 3-4Å (ref. 10). This allows significant interaction between π-molecular orbitals of stacked molecules, some of which are present as radical-ions, and results in conductivity along the stack.



(22)

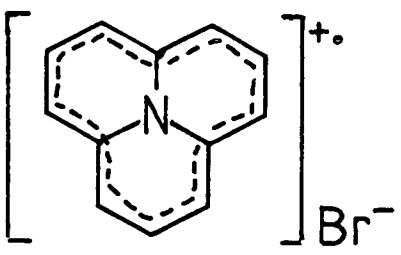


(23)

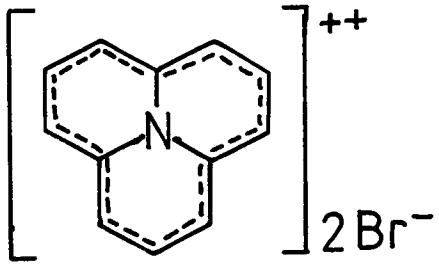
Most of the research on donor molecules has involved sulphur- or selenium-based heterocycles with extended π-networks[11,12]. The large heteroatoms provide ample opportunity for the intermolecular orbital interactions necessary for high conductivity, and some of the radical-cation salts of these molecules become superconducting in the temperature range 1-10K. Nitrogen-based donor molecules have not been investigated to the same extent because of the disappointing results obtained in initial experiments. It now seems possible, however, that the low conductivities observed were due to the choice of N-heterocycles with inappropriate reduction potentials (for the process $D^+ + e \rightarrow D^\circ$).

The use of cyclazines and their related doubly-N-bridged annulenes as the donor components in charge transfer complexes is not as yet documented, but they are likely to be more effective than previously-studied N-donors because a) they are planar, conjugated molecules and can be synthesised free from bulky substituents which may prevent the molecular orbital proximity required for conductivity; b) substituents containing sulphur or selenium could be readily introduced, if required, to increase intermolecular interaction[13,14]; c) they are known, or are expected to form stable radical-cations on oxidation[6]; d) their ionisation energies vary widely with structure, leading to the possibility of optimisation of donor properties.

As already mentioned, solution oxidation reactions have been carried out on (3) using bromine vapour[6], resulting in the air-stable blue solid with structure (24), identified by e.s.r., elemental analysis and by its conversion, on further treatment with bromine, to (25) which was characterised by n.m.r. but could not be recrystallised owing to its hygroscopic nature.



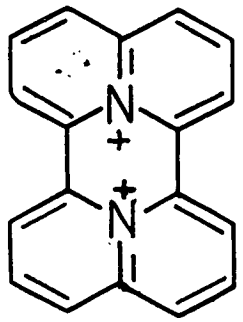
(24)



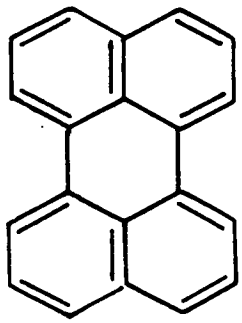
(25)

The 1,3-diaza[3.3.3]cyclazine (21) would be expected to be more stable than the parent compound (3) owing to a greater ionisation energy, and should therefore be of improved suitability for use in organic metals.

Compound (20) is, as yet, unknown, but it is to be expected that it will be oxidisable *via* a stable radical cation to a dication (26). Both the parent (20) and the dication (26) would be aromatic; the parent because of its [18]-annulene perimeter and (4n+2) π-electrons, and the dication because it is isoelectronic with perylene (27), a hydrocarbon which has been used as a donor component in organic metals.



(26)



(27)

The study of organic materials showing interesting electrical properties is an area of rapid growth because the potential for applying the knowledge derived from these studies to the next generation of electronic devices and energy conversion systems is enormous. The target compounds (20) and (21) are therefore of considerable practical as well as academic interest because of their envisaged ability to exhibit the properties required of donor molecules in charge-transfer complexes.

SYNTHETIC APPROACHES TO TARGET COMPOUNDS

Retrosynthetic analysis of the two target compounds led to a key disconnection, depicted in Fig. (2) and a synthon requiring 4,6-disubstitution of a quinolizine nucleus (28).

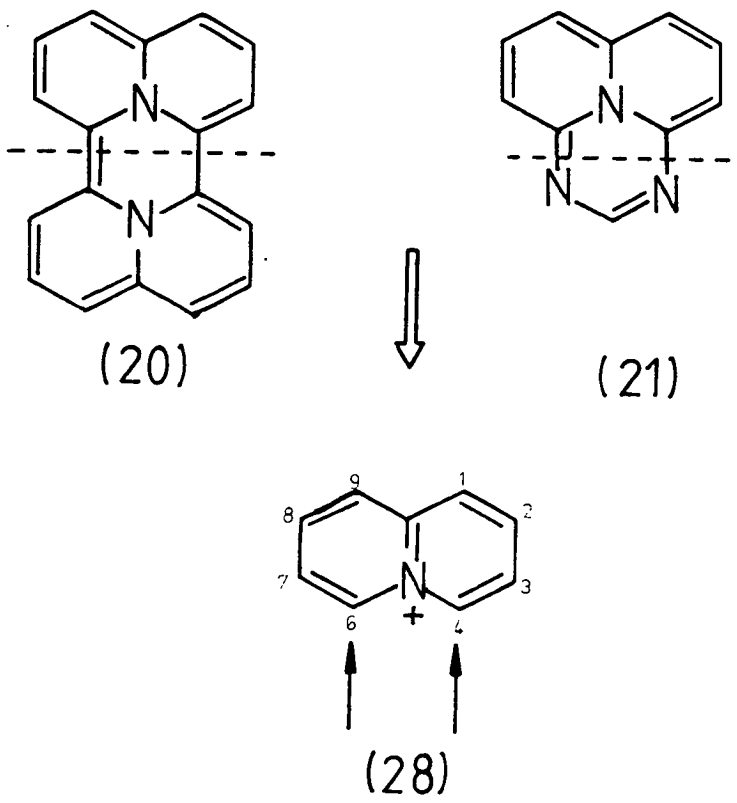
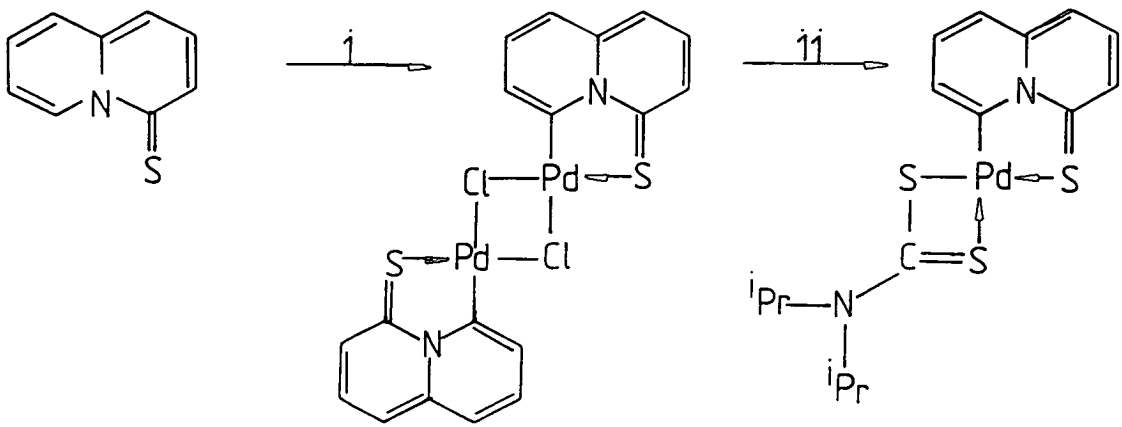
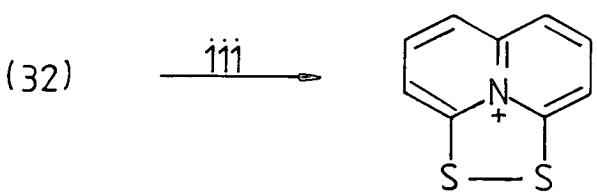


Fig.(2)

Although the quinolizine nucleus and its 4-substituted derivatives are familiar and well-documented (see later), the 4,6-disubstituted analogues are much less common and a more problematic synthetic target. In order to achieve the required substitution pattern, this work utilized cyclopalladation of quinolizine-4-thione (29), a method established by O'Neil[15]. The palladium moiety was



(29) (31) (32)



(32) (30)

i Na_2PdCl_4

ii $(^iPr)_2NCS_2^-Na^+$

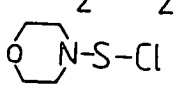
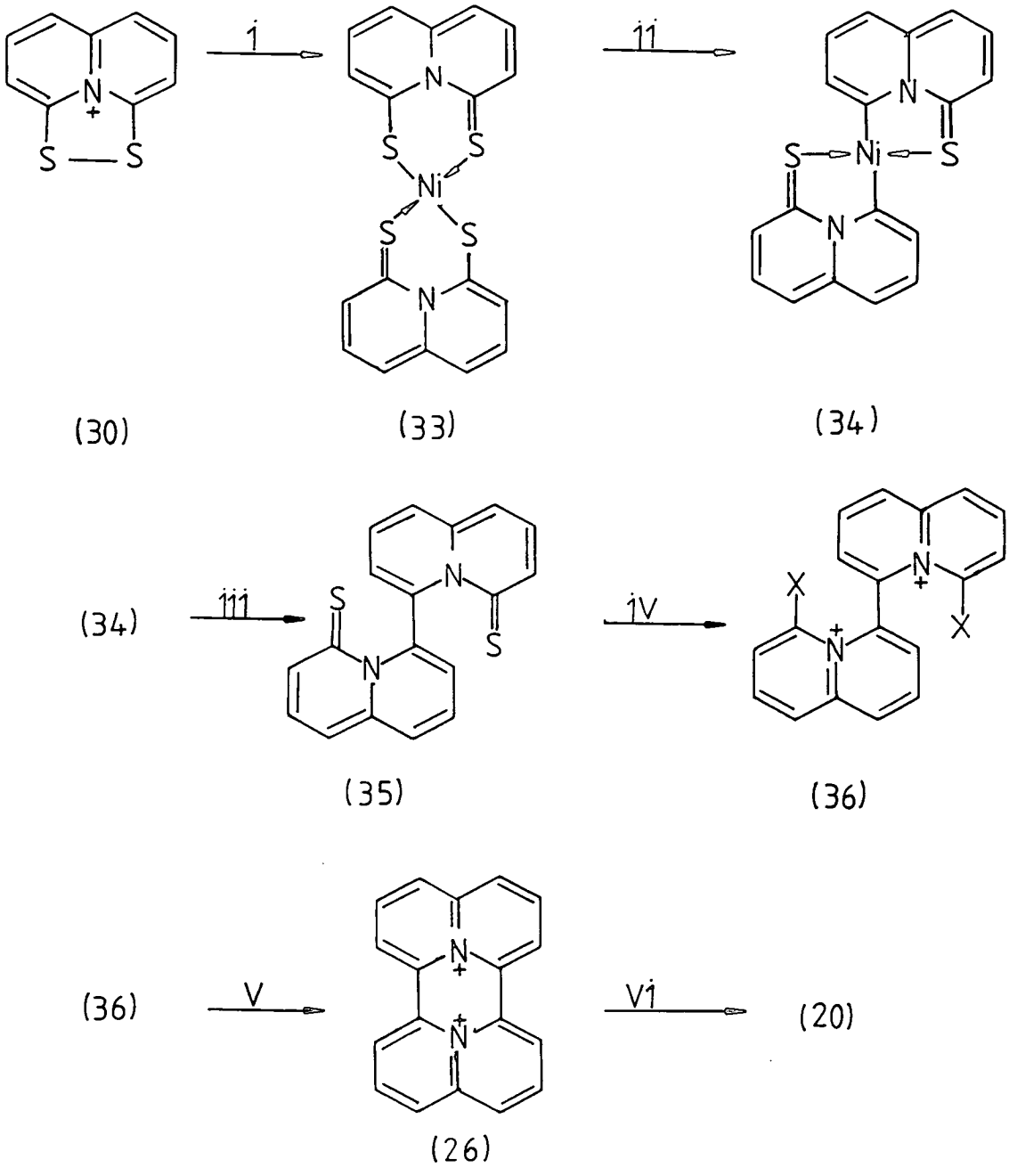
iii 

Fig (3)

subsequently replaced as shown in Fig. (3) to obtain [1,2,4]-dithiazolo[3,4,5-*de*]quinolizinium perchlorate (30), containing the desired synthon (28). The envisaged routes from (30) to (20) and (21) are shown in Figs. (4) and (5) respectively.

The preparation of the salt (30) is documented[15]. Incomplete evidence exists for the subsequent two steps in Fig. (4) but thereafter, there are no reports of investigation.



i $NaBH_4$, Ni^{2+}

ii Δ

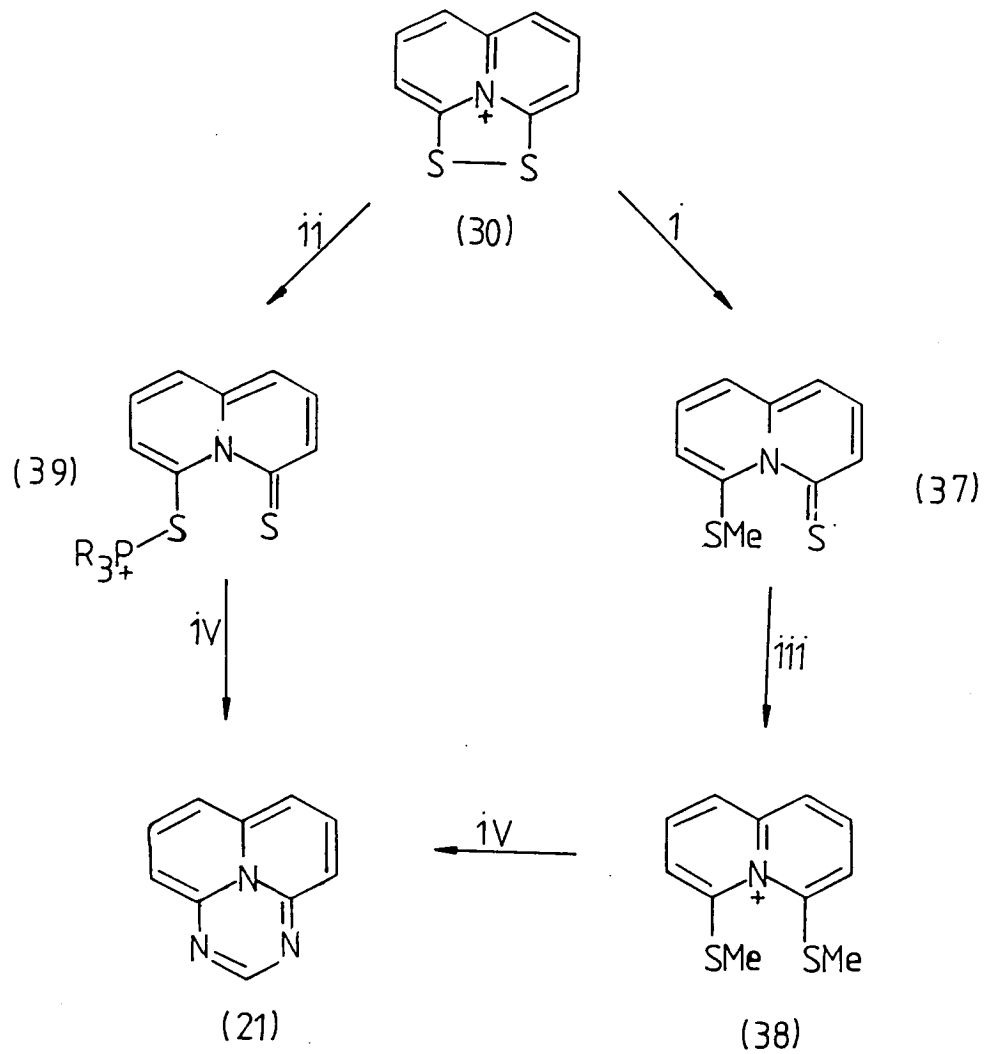
iii $-Ni^{\circ}$

iv $POBr_3$

V Zero Valent Metal (Zn,Cu or Ni)

vi Reduction ($+2e^-$)

Fig.(4)



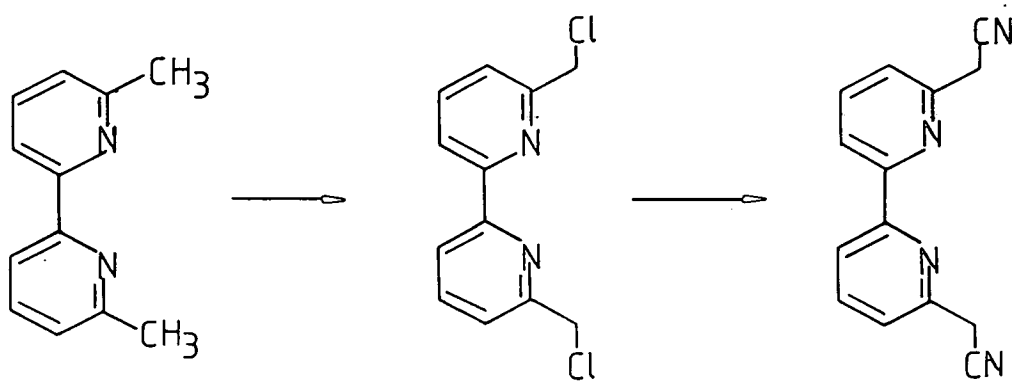
i $Na_2S_2O_3$, MeI

ii R_3P

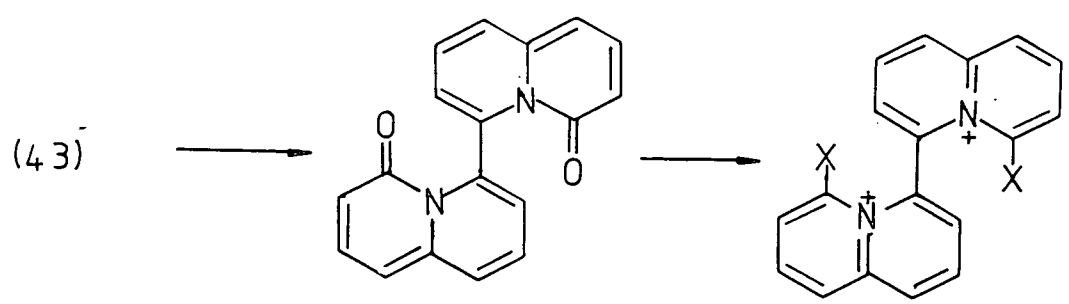
iii MeI

iv $H_2N{-}CH{=}NH$

Fig. (5)



(41) (42) (43)

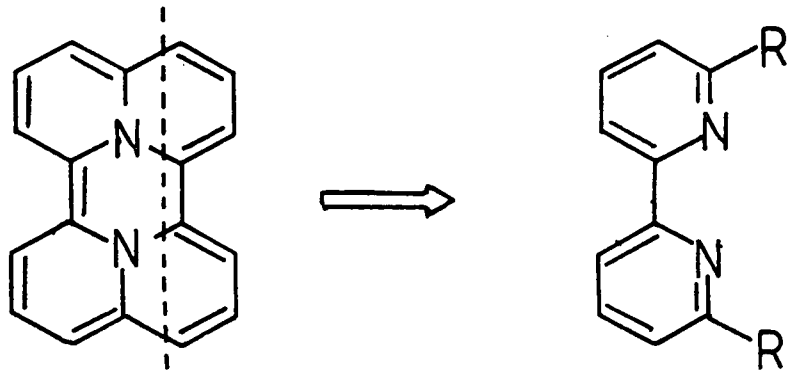


(44) (36)

(36) → (26) → (20)

Fig.(7)

In tandem with this approach from a quinolizine synthon, an alternative disconnection of the doubly N-bridged annulene (20) was envisaged as shown in Fig. (6), leading to 6,6′-disubstituted-2,2′-bipyridines (40) as starting materials, and a ring-building approach analogous to that commonly utilised in the synthesis of quinolizine nuclei Fig. (7).

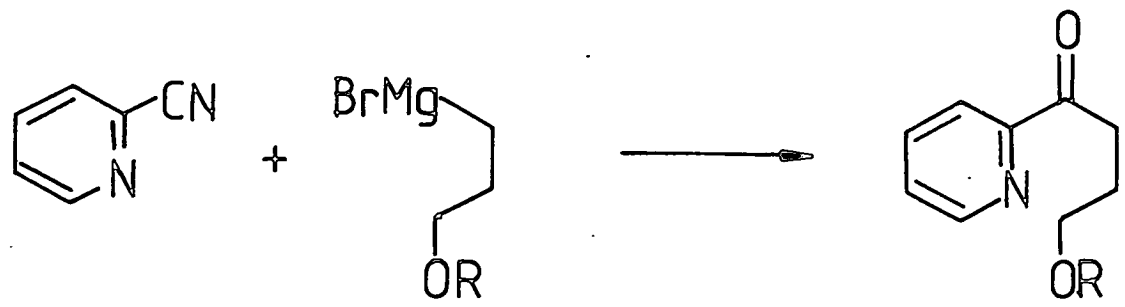


(20) (40)

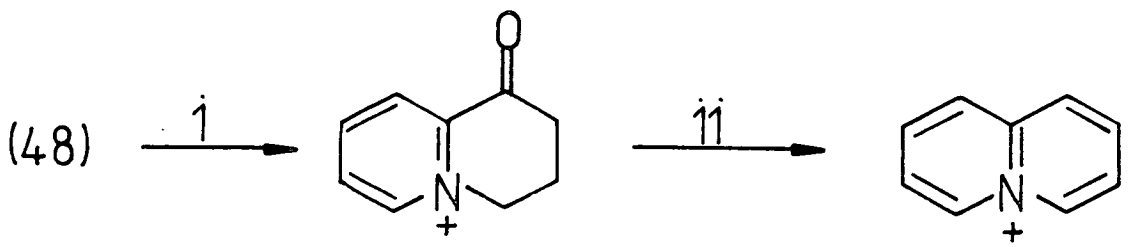
Fig. (6)

Fig. (7) outlines only our original approach to the required ring system. Many alternative routes to the quinolizine nucleus exist, some of which could be applied to our attempted synthesis of a 6,6′-bis(quinolizine) system. These alternatives will be dealt with in the discussion section.

The remainder of the introduction contains accounts of some aspects of heterocyclic reactivity and methodology which are relevant to the foregoing proposed strategies.



(47) (48)



(49) (46)

i $HBr, CHCl_3$

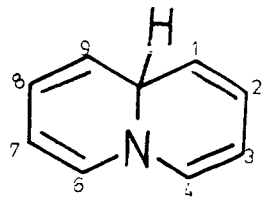
ii Ac_2O

Fig. (8)

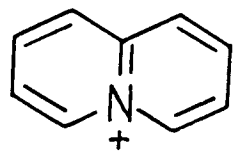
QUINOLIZINES AND RELATED COMPOUNDS

This topic was recently reviewed by Jones[16] and the following description serves to highlight work of particular relevance to this project.

Quinolizines are non-aromatic molecules which can exist in three tautomeric forms, the 9aH-(45), 2H-, and 4H- quinolizines. They are not known in unsubstituted form but the aromatic quinolizinium ion (46), in principle derived from the quinolizines by loss of a hydride ion, is a stable entity and the simplest known member of the series.



(45)

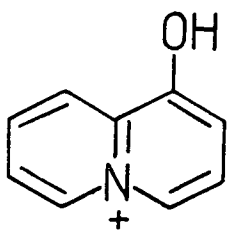


(46)

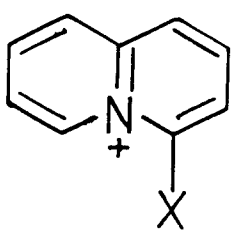
Early syntheses of quinolizinium ions involved the condensation of 2-picolyl-lithium with β-alkoxy-acroleins[17b], β-dialkoxyketones[17b,18,19] or β-alkoxyketones[18,20]. In addition, Westphal and Feix[21] used the condensation of 1,2-diketones with N-methylene-2-picolinium salts to synthesise 2,3-disubstituted quinolizinium ions. However, these methods were generally problematic and low-yielding. In 1958, Glover and Jones[22] devised a novel approach to the quinolizinium ion, outlined in Fig. (8). Because it is not subject to the

aforementioned limitations, this method is now widely used in the synthesis of quinolizinium ions.

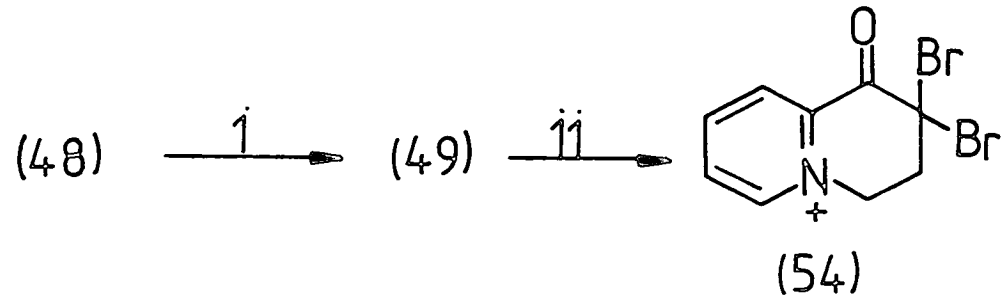
For the objectives of this work, quinolizine nuclei with a) minimal substitution and b) capability for 4,4'-coupling are required. Examples of compounds meeting these requirements are 1-hydroxyquinolizinium ion (50), quinolizine-4-thione (29) and 4-halogenoquinolizinium ions (51). In the case of (50), oxidative methods could possibly be used to effect the desired coupling, whereas metallic copper, other transition metals, or their zero-valent complexes would be possible reagents for the coupling of (29) and (51).



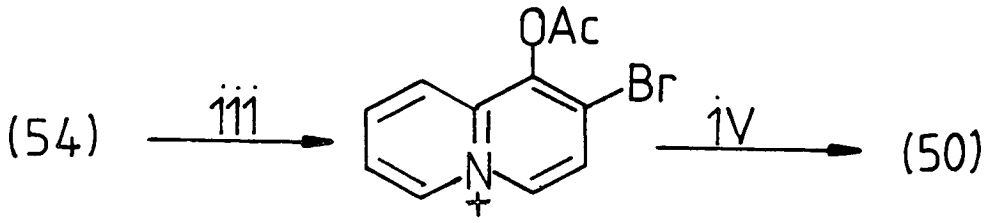
(50)



(51)



(54)



(55)

i HBr

ii HBr/Br_2

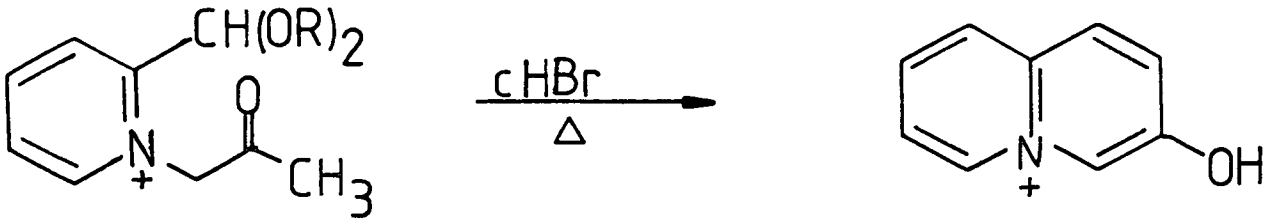
iii Ac_2O

iv Hydrogenolysis

Fig.(10)

Hydroxyquinolizinium Salts

These were first reported by Schraufstätter[23] who synthesised the 3-hydroxy form according to Fig. (9).

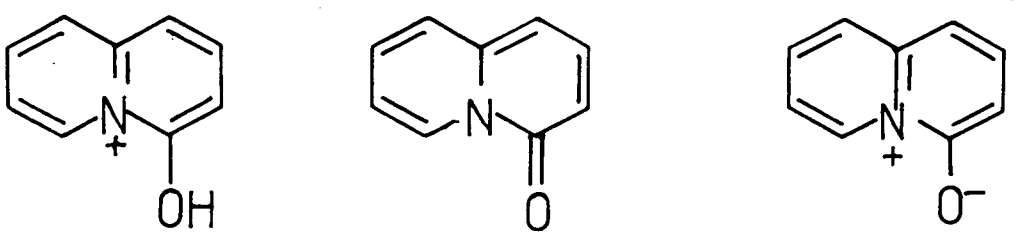


(52) (53)

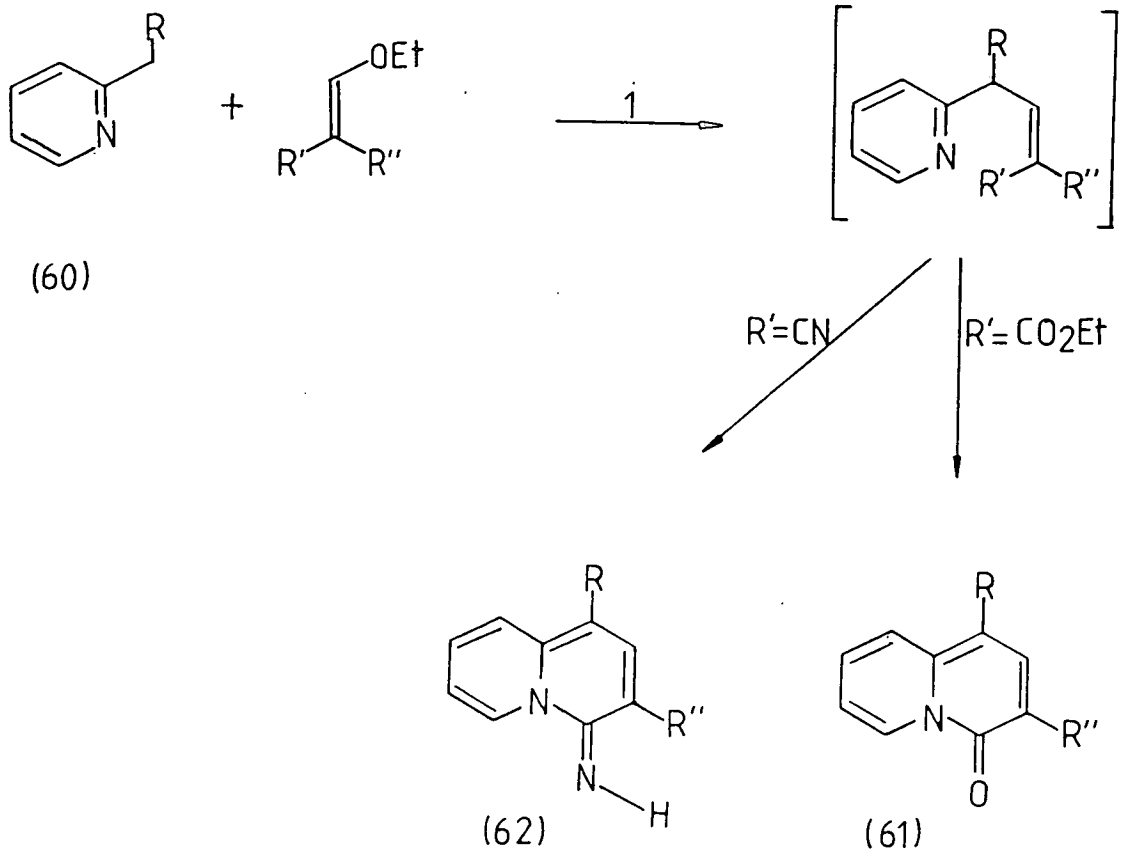
Fig. (9)

Duke *et al.*[24] also used this intramolecular aldol approach to the 3-hydroxy derivative, having previously synthesised the 1-hydroxy compound (50)[25] according to Fig. (10).

2- and 4-Hydroxyquinolizinium ions[26,27] are the conjugate acids, respectively, of quinolizin-2- and -4-ones which are best regarded as resonance hybrids with contributions from both uncharged [e.g. (57)] and zwitterionic [e.g. (58)] structures.



(56) (57) (58)

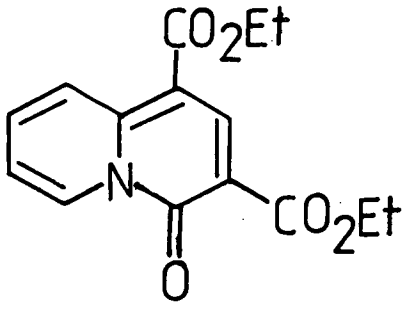


1 Base

11 TsOH

Fig. (11)

The first reported synthesis of quinolizin-4-ones was that of Clemo and co-workers[28] and the parent (57) was obtained by Boekelheide[27] by means of hydrolysis and decarboxylation of the 1,3-di(ethoxycarbonyl)derivative (59).



(59)

Many approaches to the quinolizin-4-one nucleus are documented[16], but in general the most successful methods can be described by Fig. (11). Activation of the 2-picoline (60) can be supplied by ester[29,30], cyano[31] or ketone[30,32] groups. Substituents on the ethoxymethylene component can be ester[29-32], nitro[30], cyano[30], ketone[30-32] or 2-pyridyl[31], but in most cases one of the groups R′ or R′′ is an ester, which cyclises onto the pyridine nitrogen atom, giving rise to the 4-carbonyl moiety. However, cyclisation of a nitrile can occur to give a quinolizine-imine (62) as also shown in Fig. (11). Examples of this process have been reported where R was cyano, ester[31,33], or ketone[31] and R′′ was phenyl, 2-pyridyl, ketone, ester[31] or cyano[31,33].

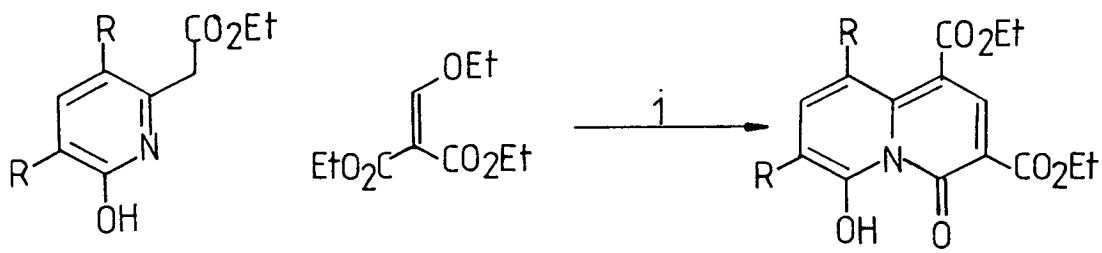
The action of the Horner-Wittig reagent (64) on

2-formyl pyridine (63) was reported[34] to give the stable product (65) which was readily converted into (66) by acid-catalysed cyclisation.

6-Substituted Quinolizin-4-ones

The introduction of substituents into the non-oxygenated ring of quinolizin-4-ones can be attained by using suitably-substituted pyridyl starting materials. However, these reactions may result in side products[31] or low yields[31,34,35] especially where 2,6-disubstituted pyridines are used.

Adams and Reifschneider[36] synthesised (68a) according to Fig. (12), but the starting material (67a) was itself the product of several stages of synthesis. This strategy was later modified by Leaver and co-workers[37] who obtained the starting material (67b) from diethyl β-amino-glutaconate and diethylethoxymethylenemalonate. Unfortunately the 6-hydroxy substituent of (68b) was not amenable to methylation, sulphonation or replacement with a chlorine atom.

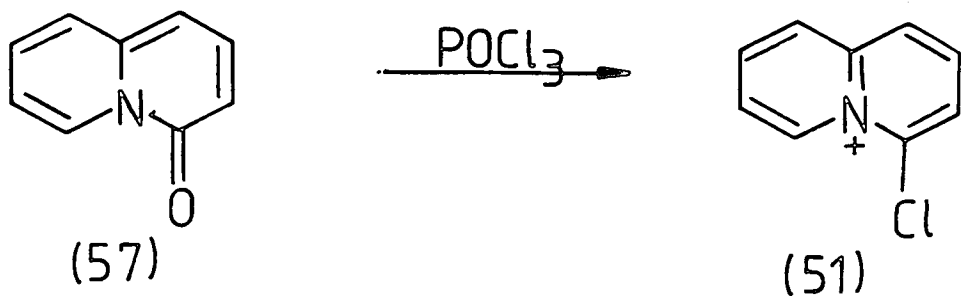


(67) a:R=H
b:R=CO_2Et

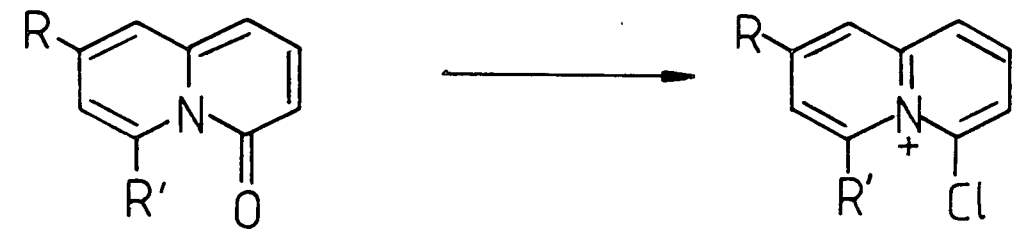
(68) a:R=H
b:R=CO_2Et

1 Base

Fig.(12)

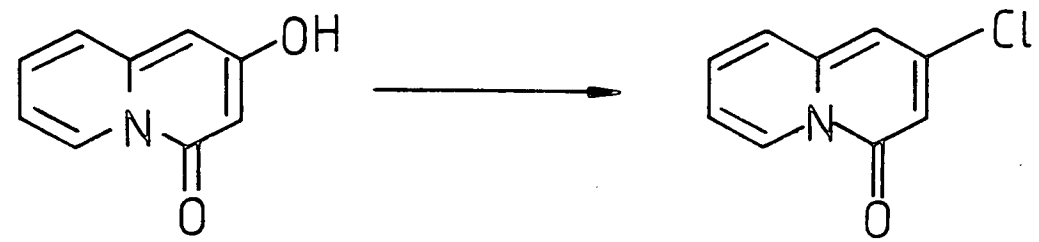


(57) (51)



R=H, R'=Me (71)
R=Me, R'=H (72)

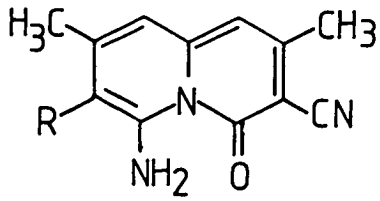
(73)
(74)



(75) (76)

Fig.(13)

Van Allan and Reynolds[38] synthesised the highly substituted quinolizin-4-ones (69) and (70), but could not effect subsequent displacement reactions of the amino substituent.



(69) R=CN
(70) R=$CONH_2$

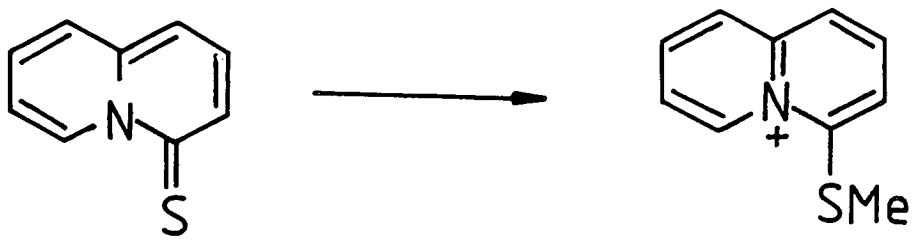
Reactions of Quinolizin-4-ones

These have been comprehensively reviewed by Jones[16] and only those reactions of direct relevance to the current work will be described here.

Quinolizin-4-one (57) has been converted to the 4-chloroquinolizinium salt (51) by treatment with phosphoryl chloride, as have the 6- and 8-methyl derivatives (71) and (72)[39]. However, 2-hydroxy-quinolizin-4-one (75) forms the 2-chloro- compound (76) preferentially[40] as outlined in Fig. (13).

Synthesis of quinolizine-4-thione (29) from quinolizin-4-one (57) was achieved in 1951 by Boekelheide[27] using phosphorus pentasulphide. This method was subsequently improved by Van Allan and Reynolds[39] who proceeded *via* the 4-chloroquinolizinium salt (51) to the thione (29) by treatment with sodium sulphide.

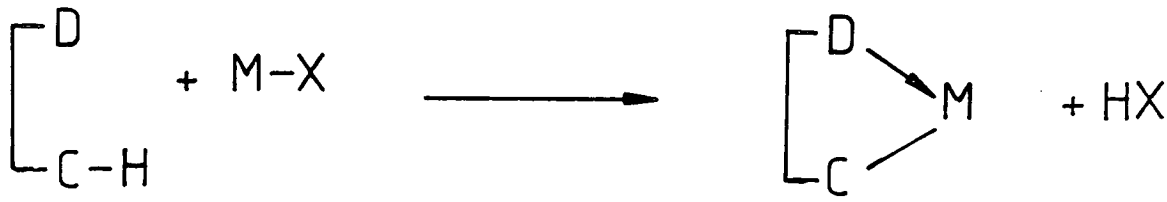
Methylation of quinolizine-4-thione (29) is possible using methyl iodide[41] or dimethyl sulphate[39] and leads to the 4-methylthioquinolizinium salt (77).



(29) (77)

CYCLOPALLADATION

The term cyclometallation was first used by Trofimenko[42] to describe the transition metal complex reactions in which a ligand undergoes an intramolecular metallation with the formation of a chelate ring containing a metal-carbon sigma bond. The general reaction is illustrated in Fig. (14).



D=Donor Atom

M=Transition Metal

X=Leaving Group

Fig.(14)

The substrate ligand most commonly has the ability to form a five-membered chelate ring as in Fig. (15).

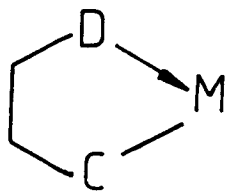
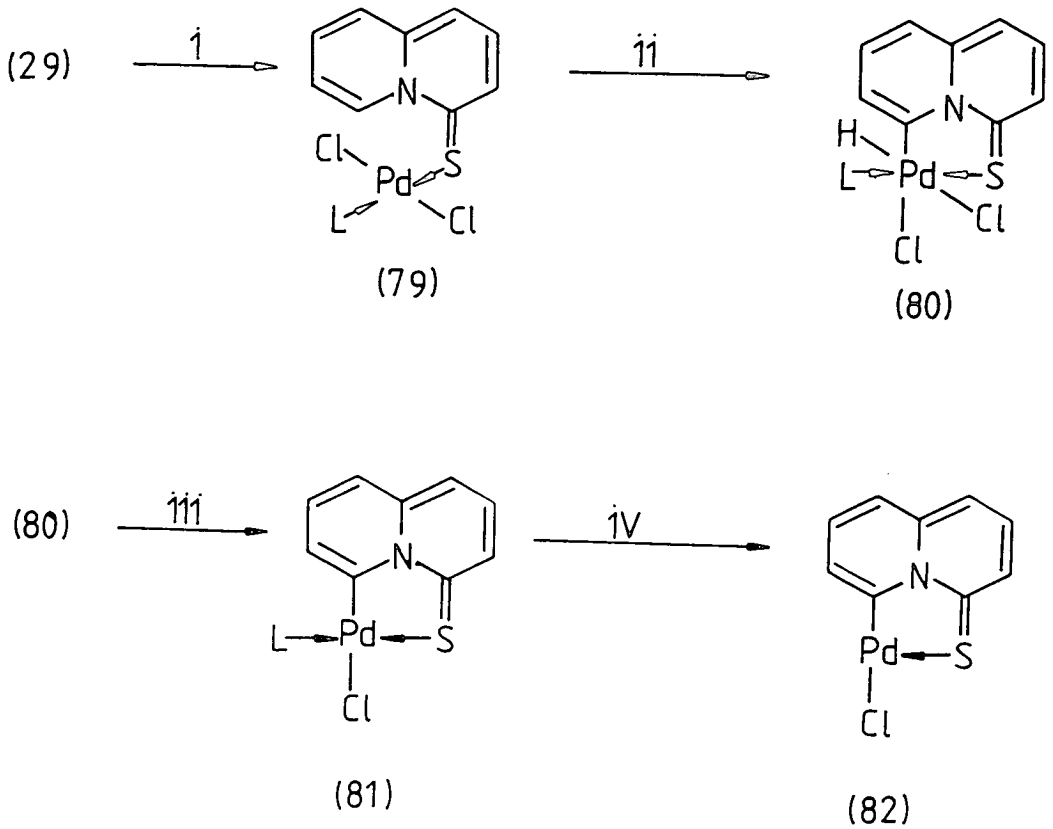


Fig.(15)

Such ligands are classified according to the type of donor atom which may be nitrogen, sulphur, oxygen, phosphorus or arsenic. Only examples where the donor atom is nitrogen or sulphur and the metal is palladium will be considered in the following short discussion.

Extensive studies[43,44] led to the proposal of an electrophilic mechanism for cyclopalladation, i.e. initial



2 x (82) ⟶ (31)

i Na_2PdCl_4

ii Oxidative Addition

iii Reductive Elimination

iV Loss of Substrate (L)

L=

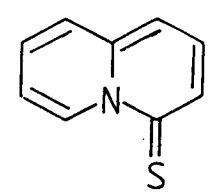
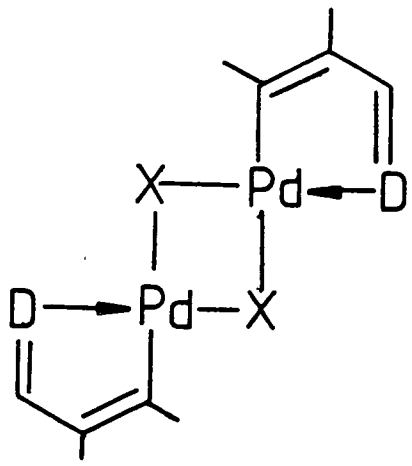


Fig.(16)

rapid co-ordination of the ligand to the metal *via* the donor atom, followed by weak electrophilic attack by the co-ordinated palladium on the aromatic ring in the ligand resulting invariably in a chloride- or acetate-bridged dimer of the general structure (78).

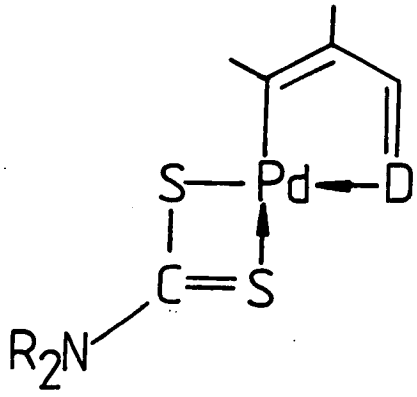


(78) X=Cl or OAc

However, the specific cyclopalladation used in this work employed quinolizine-4-thione (29) as the substrate ligand, sulphur being the donor atom, and O'Neil[15] suggested that the mechanism of this reaction was not electrophilic in nature. Such a pathway, he argued, would be unfavourable owing to the electron-withdrawing effect of the thiocarbonyl, causing deactivation of the carbon atom at position 6 to electrophilic attack. The alternative mechanism postulated is outlined in Fig. (16). The first step is co-ordination of two substrate ligands onto palladium. The second step is oxidative addition as a result of insertion of palladium into the carbon-hydrogen bond at position 6. Reductive elimination

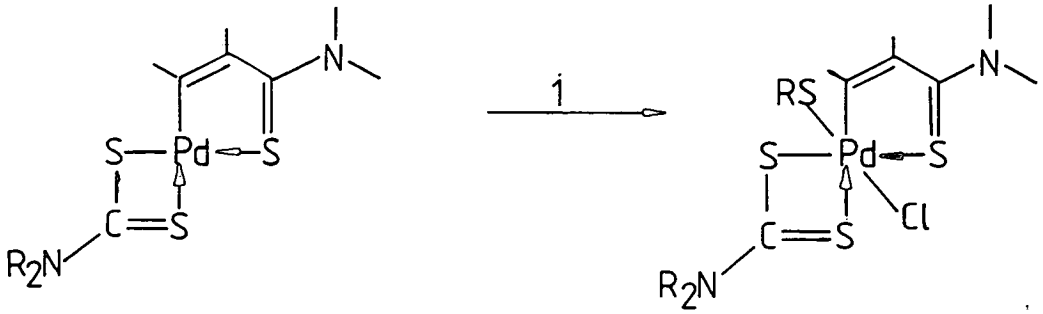
of hydrogen chloride is then followed by the loss of a substrate ligand. The resulting co-ordinatively unsaturated species (82) then dimerises to form (31).

The chloride-bridged dimers (78) formed by cyclopalladation are generally insoluble and involatile, thus hampering identification and characterisation. However, they are known to undergo a number of reactions[15,45,46], among them, the useful bridge-splitting reaction resulting in the formation of crystalline monomeric compounds not subject to the aforementioned drawbacks. Common bridge-splitting reagents are phosphines, amines, acetylacetone and the dithiocarbamate ion. The latter reagent resulted in monomeric complexes of the type (83).

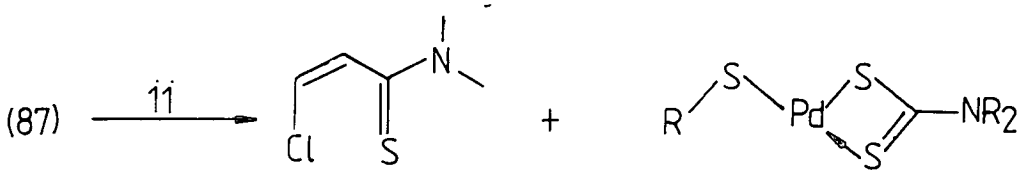


(83)

The replacement of the palladium moiety in compounds of the type (83) has been reported[15,45,46] using a variety of reagents. Of greatest relevance to this work are replacement reactions where the cyclopalladated donor



(86) (87)



(88) (89)

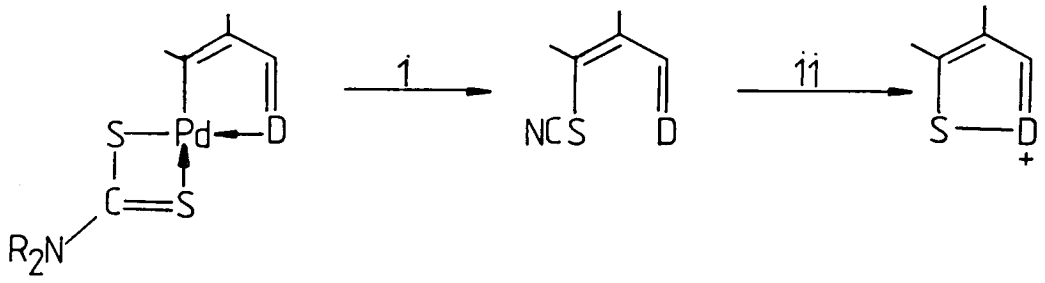
i RSCl, Oxidative Addition

ii Reductive Elimination

(90) (91)

Fig.(19)

ligand is a thioamide and the reagent has the ability to transfer sulphur. Thiocyanogen was reported as an effective sulphur-transfer reagent[45,46], leading to novel heterocyclic systems of the type (85) *via* compounds such as (84) according to Fig. (18).



(83) (84) (85)

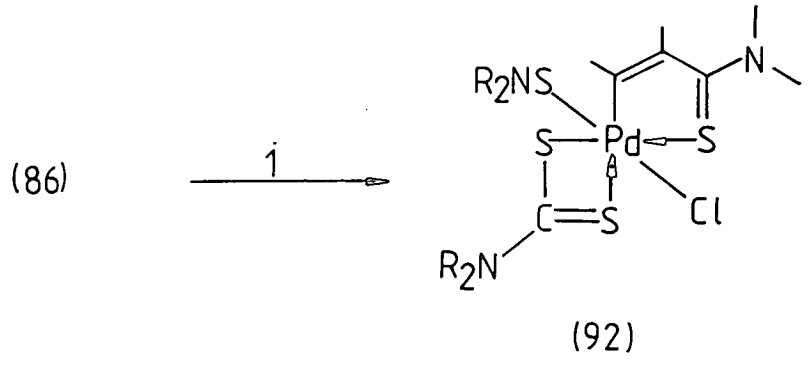
i $(NCS)_2$

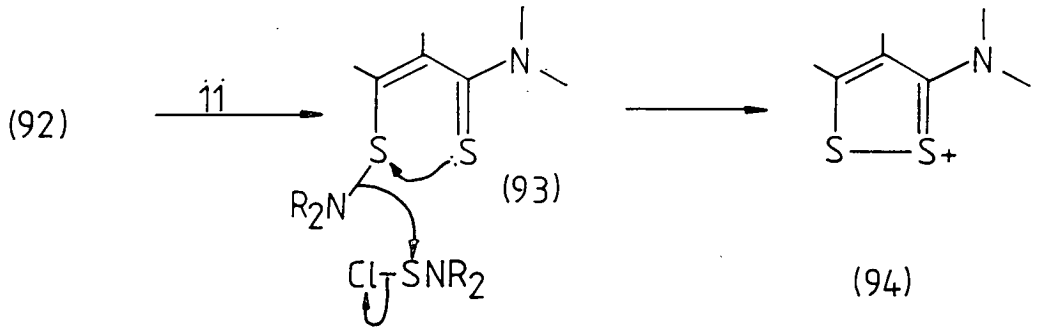
ii $HClO_4$, AcOH

Fig.(18)

However, in cases where the donor ligand was a thioamide, no such reactions were observed[46].

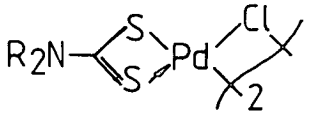
O'Neil[15] further investigated this area, trying alternative sulphur transfer reagents such as dibenzoyl disulphide, bis(amine) disulphides $(R_2NS)_2$ and bis(*p*-perthiotoluato)zinc(II), but all without success. With a view to replacing the palladium moiety with chlorine according to Fig. (19), two sulphenyl chlorides were used, *n*-butoxycarbonylsulphenyl chloride (BuO.CO.SCl) and morpholine-N-sulphenyl chloride (R_2NSCl). Because both





plus

plus



(95)

$R_2N-S-NR_2$

(96)

i R_2NS-Cl, Oxidative Addition

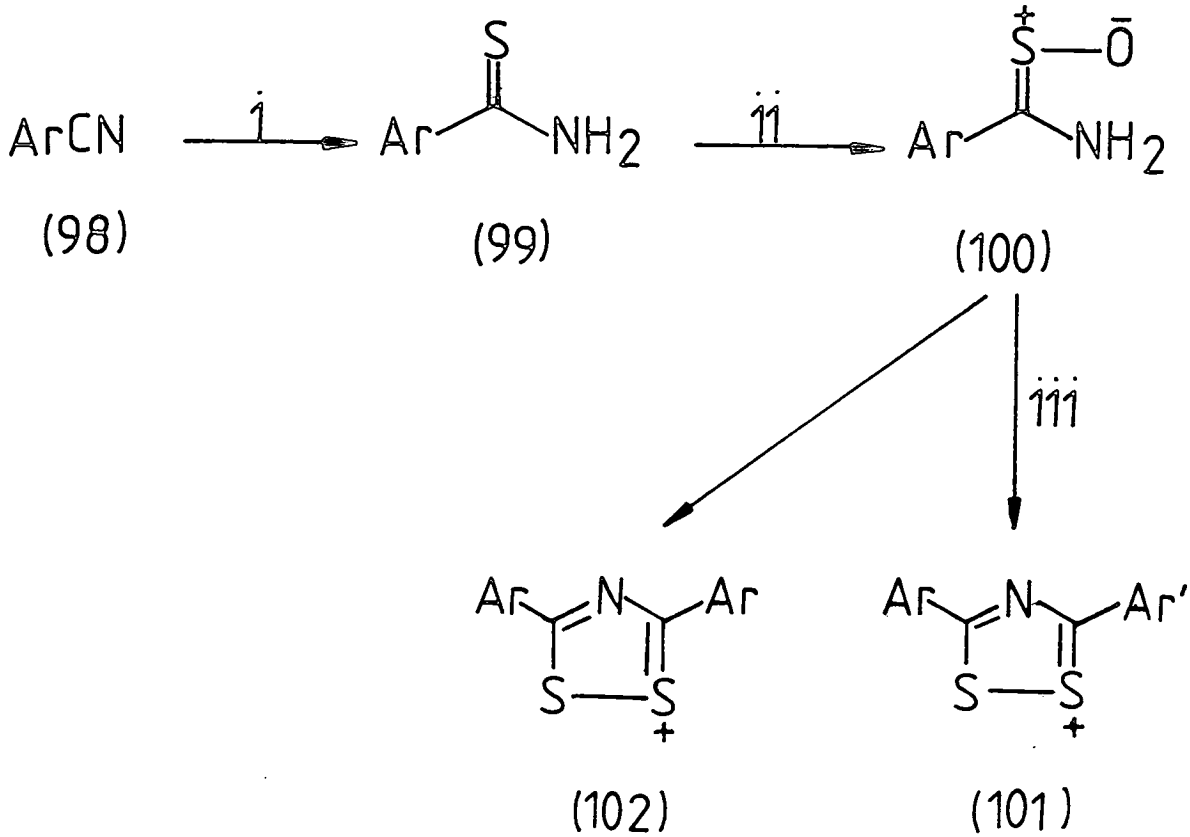
ii Reductive Elimination

Fig.(20)

reagents contain an R-group capable of transforming the RS ligand from unidentate to bidentate, it was hoped that the reductive elimination step (ii) would be encouraged to proceed in the desired manner, producing (90) and (91) respectively.

In practice, however, neither of these reactions proceeded according to Fig. (19). In the case of *n*-butoxycarbonylsulphenyl chloride, unreacted starting material was recovered[15] and morpholine-N-sulphenyl chloride effected a sulphur transfer reaction leading to a dithiolium salt (94) as shown in Fig. (20).

In the specific example used in this work, the nitrogen atom is part of the cyclopalladated ring [see structures (31),(32)] so an analogous reaction sequence to that outlined in Fig. (20) leads to the dithiazolium salt (30) rather than (94).



i H_2S

ii Oxidation (H_2O_2, X_2 or Air)

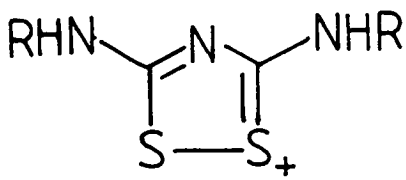
iii H^+/ Ar'–C(=S)–R (R=NH_2, NHR, SR)

Ar, Ar' may be substituted

Fig. (21)

1,2,4-DITHIAZOLIUM SALTS

These compounds were first obtained in 1947[47] as their 3,5-diamino derivatives (97).



(97)

It was not until much later[48,49,50] that a versatile method to the 3,5-di-aryl compounds (101) and (102) was established as outlined in Fig. (21). If sulphoxide (100) is isolated, and a different thioamide added, unsymmetrical 1,2,4-dithiazolium salts (101) are obtained. If the sulphoxide is not isolated, oxidation leads to the symmetrical salt (102).

However, it is not the synthesis but the reactions of these 1,2,4-dithiazolium salts with nucleophiles, as represented in general terms in Fig. (22), which are of greatest relevance to this work.

With amines[51], 1,2,4-dithiazolium salts undergo substitution of one sulphur atom to form N-thioacyl-amidines (108). These can be further transformed into thiazoles[48] (109) or thiadiazolium salts[52] (110) as illustrated in Fig. (23).

Interestingly, when the dithiazolium salt (103) counter ion is I_3^-, compounds (108) are not observed, but

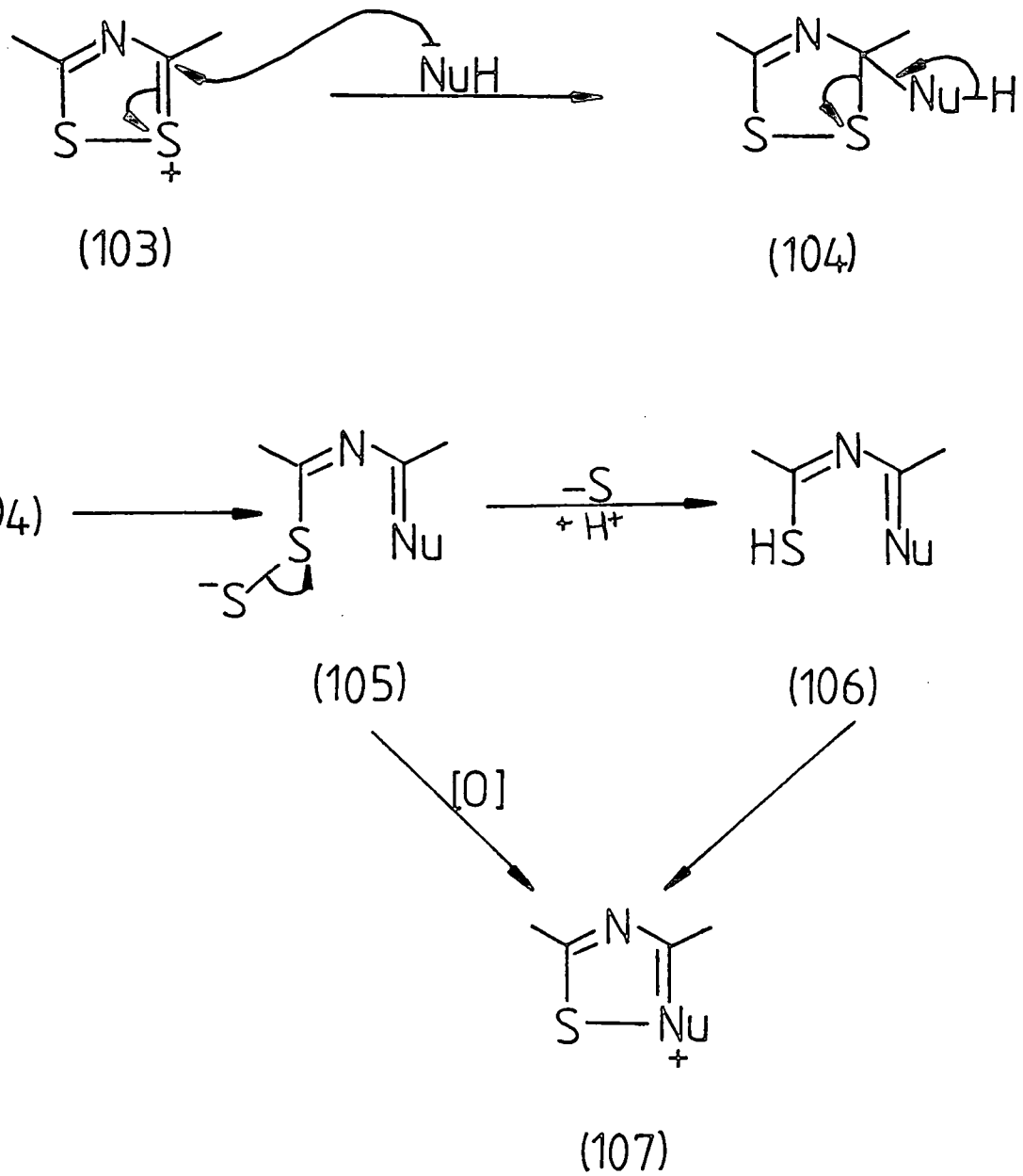
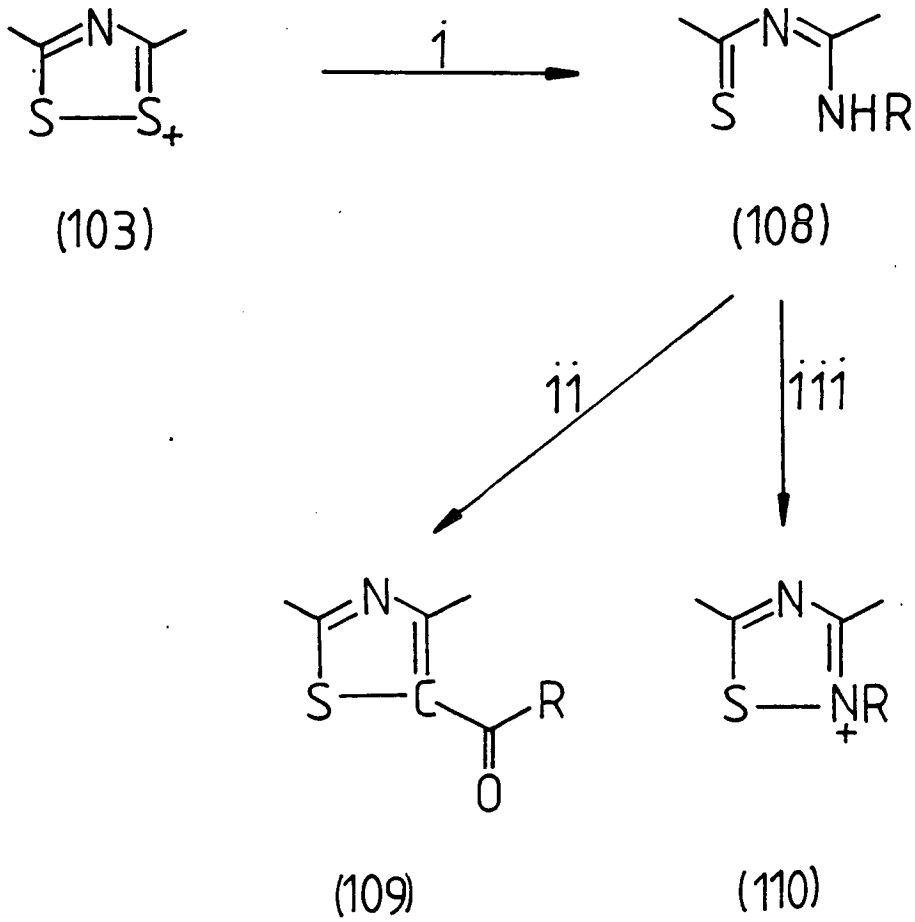


Fig.(22)



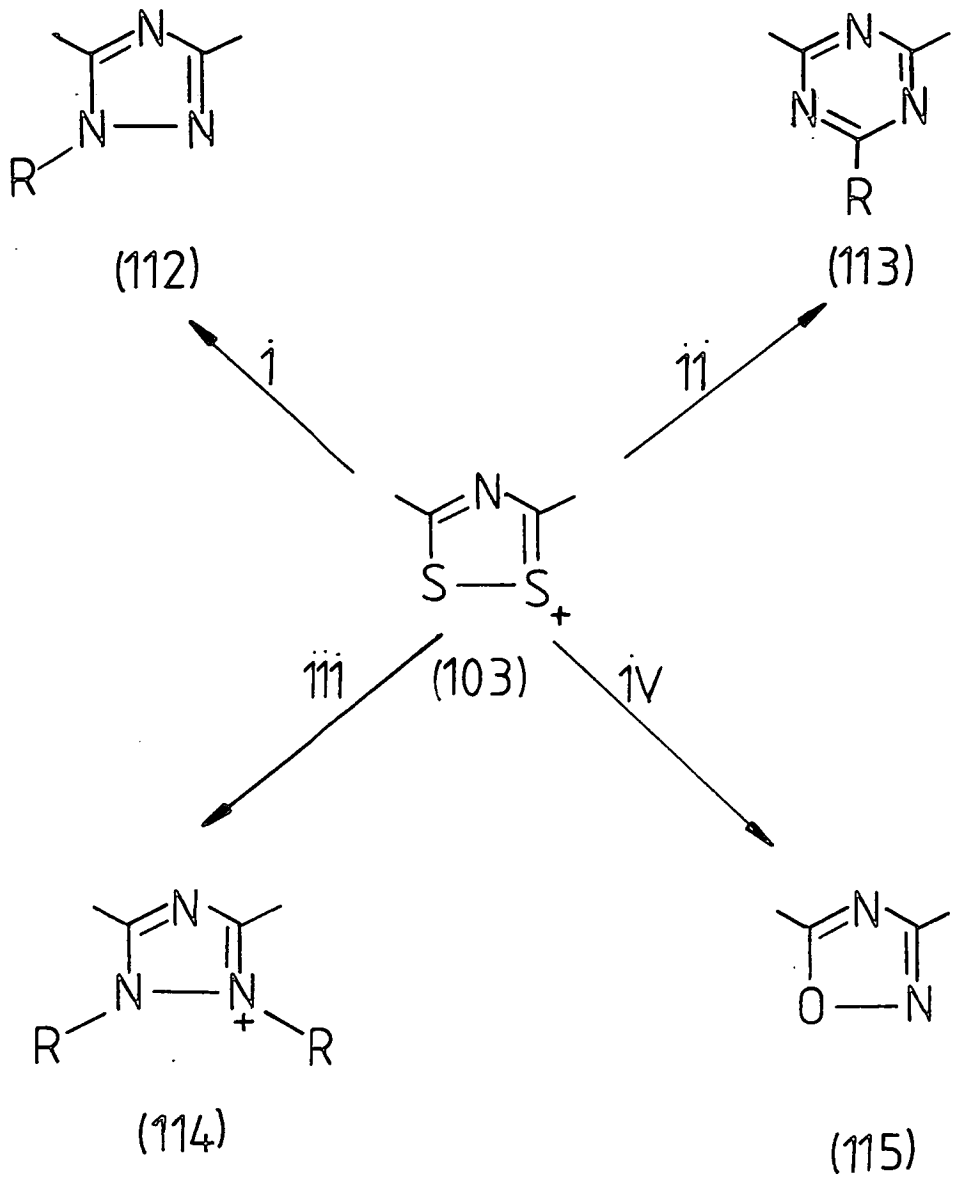
(103) (108) (109) (110)

i RNH_2

ii $RCO.CH_2Cl$

iii H_2O_2, $HClO_4$–AcOH

Fig. (23)



i H_2N-NHR

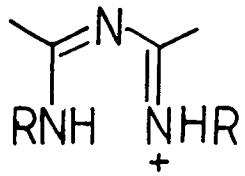
ii $RC(NH)NH_2$

iii $RNH-NHR$

iv NH_2OH

Fig. (24)

instead N-imidoylamidines (111) are obtained.

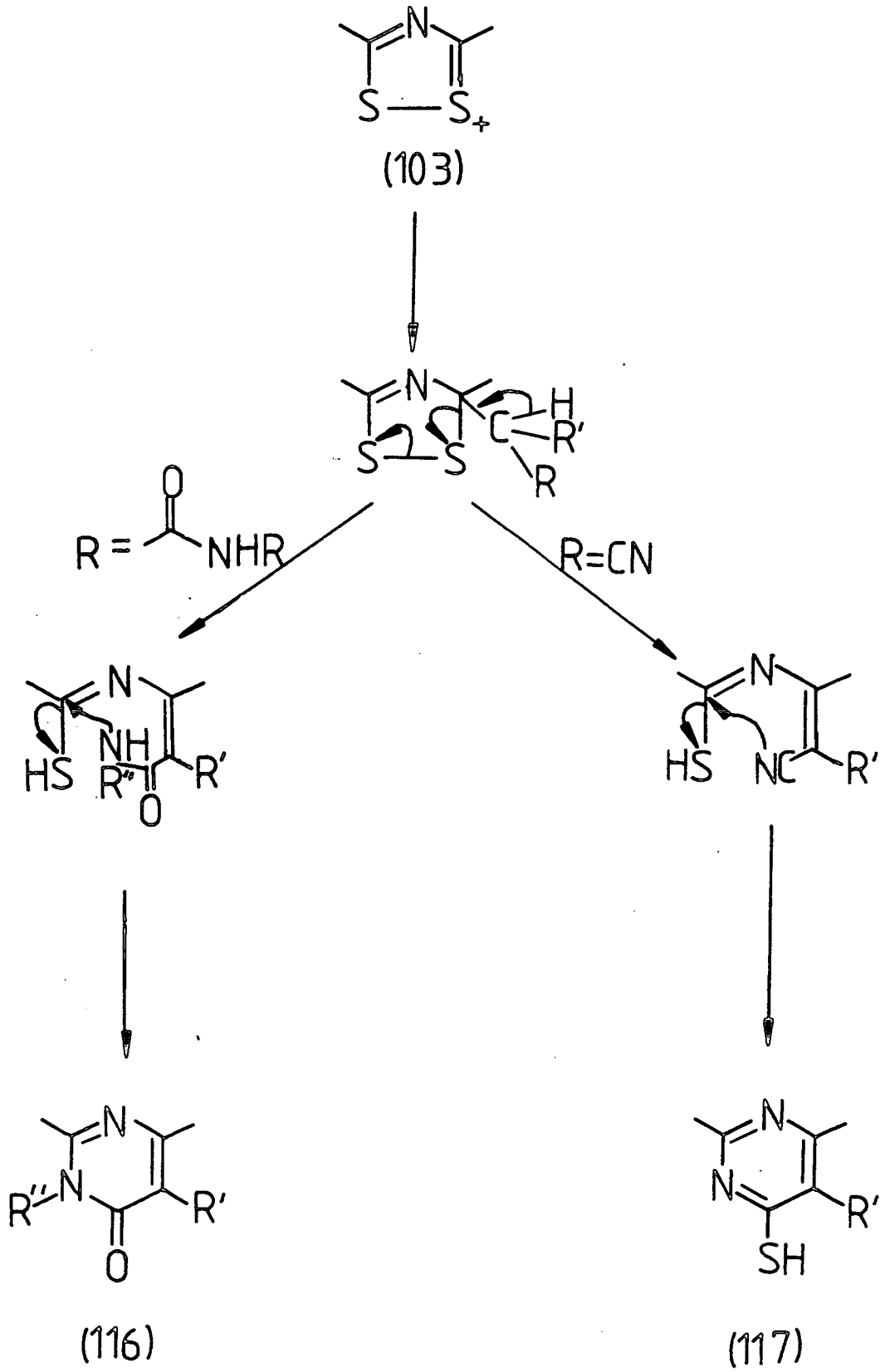


(111)

Perchlorate salts (103) and compounds (108) can be made to produce N-imidoylamidines (111) by reacting with a primary amine in the presence of an oxidising reagent. The formation of products (111) can be assumed to proceed *via* structures (108) which are oxidised to the corresponding 1,2,4-thiadiazolium salts (110). A further nucleophilic attack by the amine results in ring cleavage and substitution of the remaining sulphur atom to form the salts (111). If the analogous product types could be obtained from the [1,2,4]-dithiazolo[3,4,5-*de*]-quinolizinium perchlorate (30) they would be 4,6-difunctionalised quinolizinium salts of considerable synthetic utility in this work.

The reaction of dithiazolium salts (103) with bidentate nitrogen nucleophiles[53,54] is summarised in Fig. (24) and with active methylene compounds[55] in Fig. (25).

Reactions of dithiazolium salts (103) with thiols such as ethanethiol, thioacetates and hydrogen sulphide led to reduction products of the type (118). These compounds were found to be sensitive to aerial oxidation and could

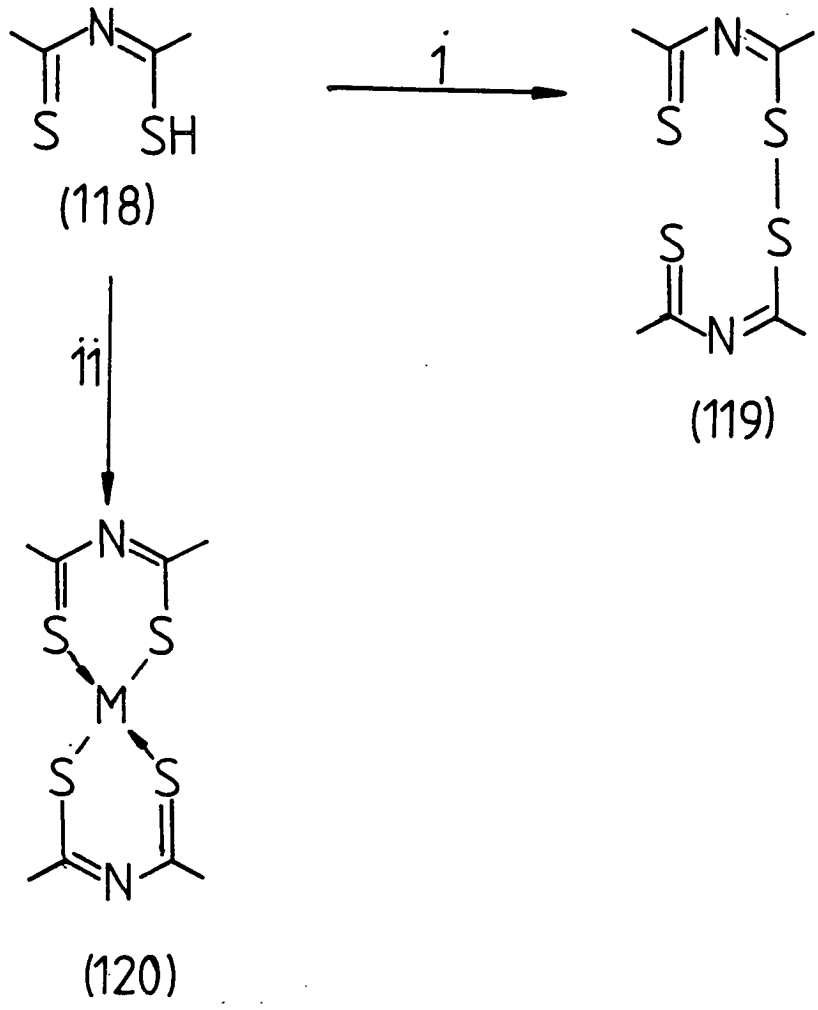


(116)

(117)

Fig. (25)

only be isolated as the disulphides (119) or trapped as complexes (120) with divalent nickel or copper as in Fig. (26).



i Oxidation

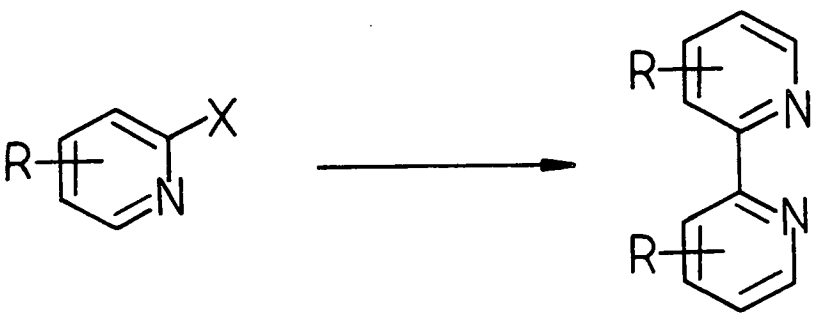
ii M^{2+}

Fig.(26)

BIPYRIDINES

This topic has been recently described in a review article by Summers[56] and the present discussion serves only to highlight those examples of specific relevance to this study, namely the symmetrically-disubstituted-2,2'-bipyridines (122).

The Ullmann reaction of substituted 2-halogeno-pyridines (121) with finely divided copper is known[57,58] but yields are variable and in the case of 6-substituted-2-halogenopyridines (121a) are unacceptably poor.



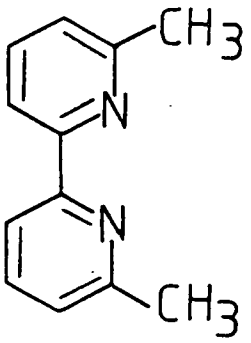
(121) a) 6-R
b) X=H
c) X=Li

(122) a) 6,6'-R
b) R=H

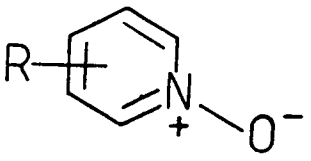
The dehydrogenative coupling of pyridines (121b) at high temperatures[59] or in the presence of degassed palladium charcoal[60] is known to afford compounds of the type (122) and (122a) but generally in low yield. The use of an oxidising agent allows the reaction to occur at lower temperatures[57,58].

Sasse and co-workers[61,62] reported the utility of degassed Raney-nickel in the formation of symmetrically-substituted 2,2'-bipyridines. They found that 3- and 4-alkyl groups in the pyridine ring facilitated the coupling, but that electron withdrawing groups in these positions, or 2-alkyl groups had the opposite effect. Thus compounds of the type (122a) could only be obtained in very low yields.

In 1978 Bamfield and Quan[63] reported a novel coupling method for 2-bromo pyridines, including 6-substituted compounds (121a), involving treatment with alkaline sodium formate in the presence of palladium charcoal and a phase-transfer catalyst. This method was successfully employed by Newkome[64,65] for the synthesis of 6,6'-dimethyl-2,2'-bipyridine (41).

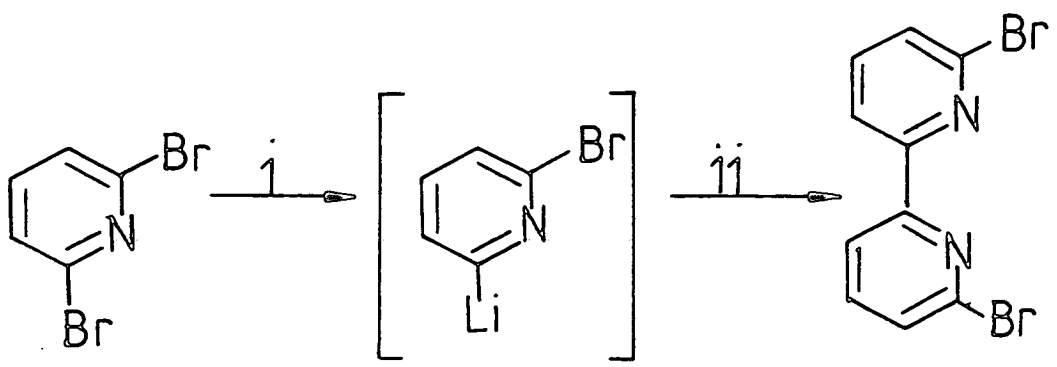


(41)



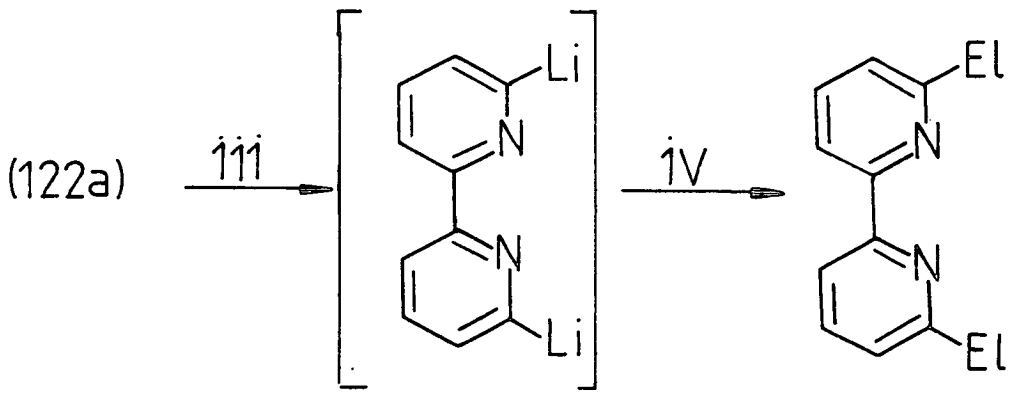
(124)

Treatment of pyridines (121b) with their corresponding N-oxides (124) in the presence of a mixed palladium/platinum catalyst has been found to produce 2,2'-bipyridines (122) in varying yields[66,67], including compounds of the type (122a)[66,68].



(125)

(122a)
R=Br



(126)

(127)

i BuLi

ii $CuCl_2$

iii 2 BuLi

iv El^+

Fig.(27)

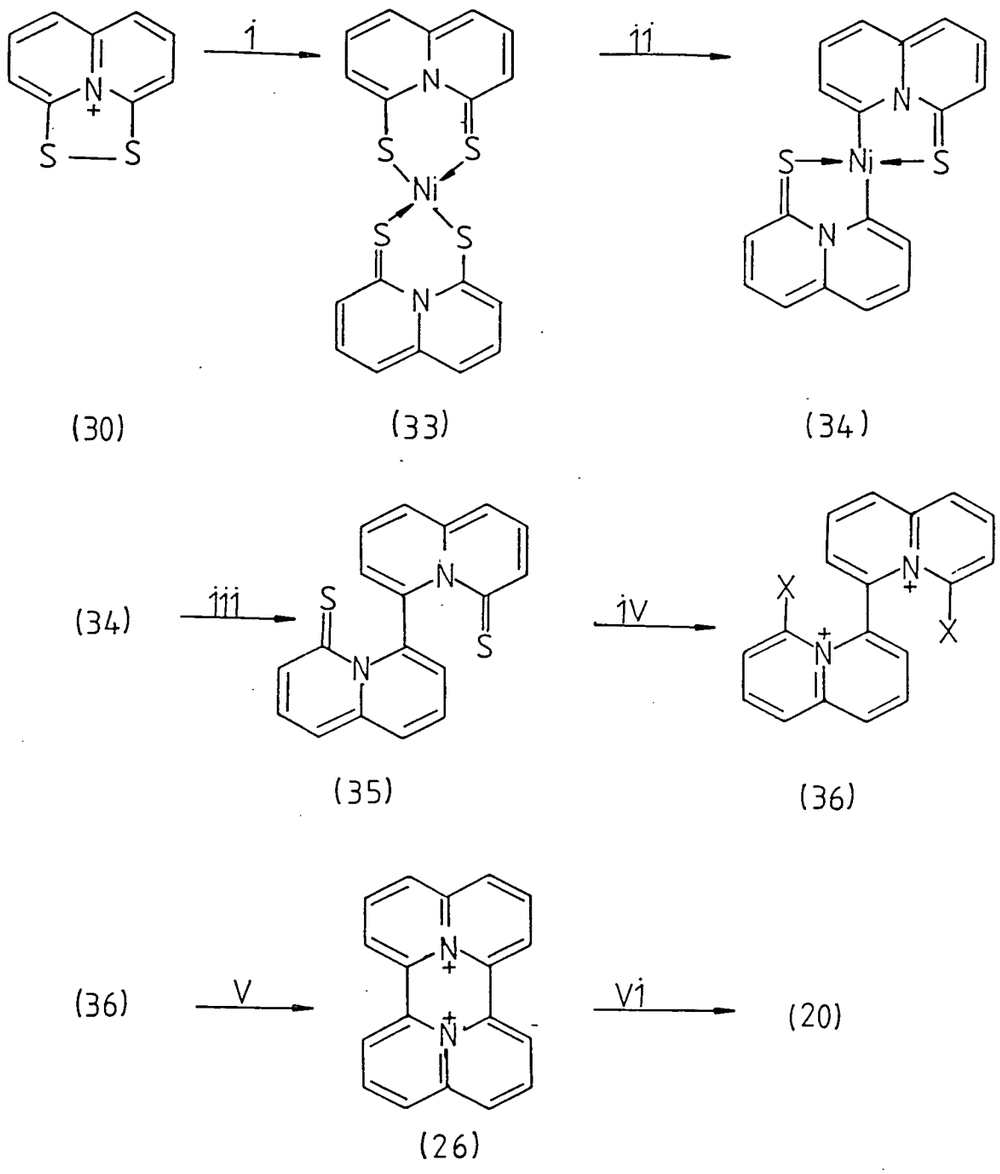
Several examples are known of 2-lithio-pyridines (121c) being coupled to form symmetrically-di-substituted-2,2′-bipyridines (122) and (122a)[70] using metal catalysts.

2,2′-Bipyridine itself (122b) can be converted into compounds of the type (122a). In 1938, Burstall[71] brominated 2,2′-bipyridine in the vapour phase at 500°C forming 6-bromo, and 6,6′-dibromo-2,2′-bipyridine (122a, R=Br). The same reaction is known for chlorine[72]. The halogen atoms in these bipyridines could then be replaced by amino, cyano, or carboxyl groups[71]. In 1973, Parks *et al.*[70] synthesised (122a, R=Br) in 50% yield from 2,6-dibromopyridine (125) and butyl-lithium. Further treatment of the product thus obtained with butyl-lithium led to the formation of 6,6′dilithio-2,2′-bipyridine (126) which was not isolated, but reacted *in situ* with a variety of electrophiles such as formyl and methyl as outlined in Fig. (27).

Direct nucleophilic substitution of 2,2′-bipyridine (122b) by alkyl and aryl groups has been achieved[73,74] by treatment with alkyl- and aryl-lithiums, leading to 6- and 6,6′-disubstituted-2,2′-bipyridines. Yields of the mono-substituted products are moderate, but those of the di-substituted products are generally very low.

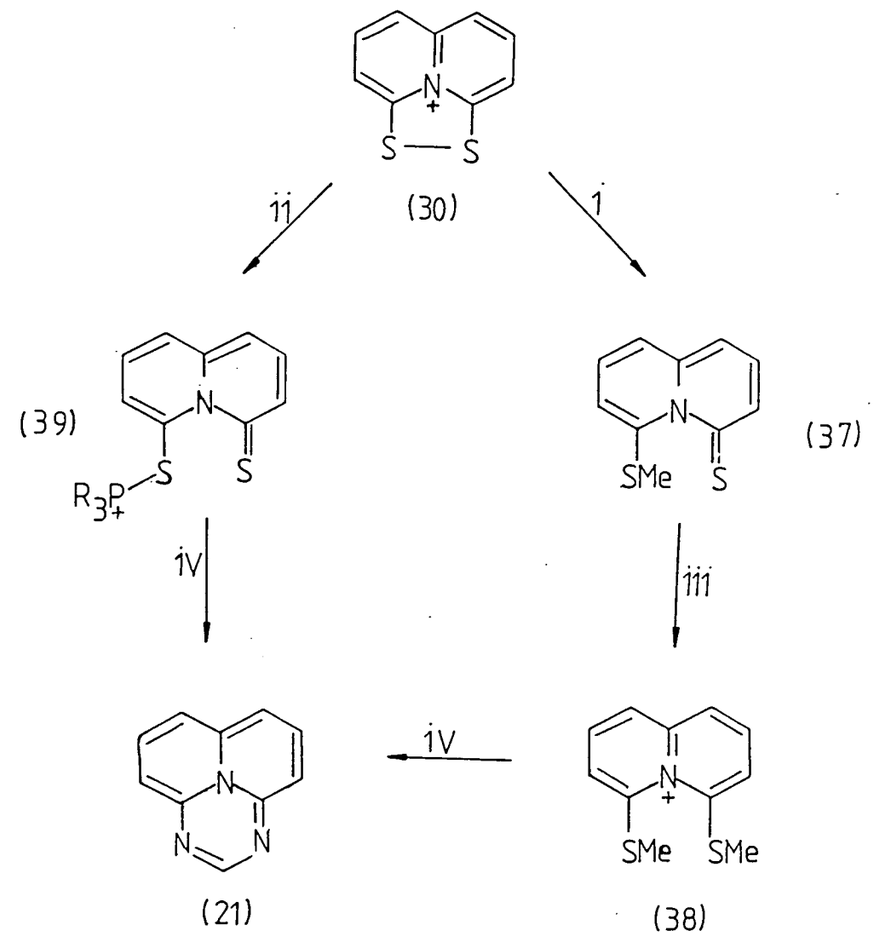
The reactions of 6,6′-disubstituted-2,2′-bipyridines are essentially those of 2-substituted pyridines and are covered in detail in the review article[56].

DISCUSSION



i $NaBH_4$, Ni^{2+}
ii Δ
iii $-Ni^{\circ}$
iv $POBr_3$
v Zero Valent Metal (Zn,Cu or Ni)
vi Reduction ($+2e^-$)

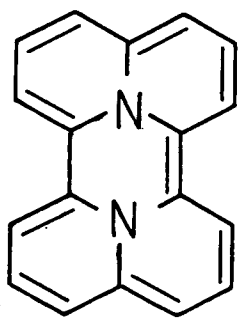
Fig.(4)



i $Na_2S_2O_3$,MeI
ii R_3P
iii MeI
iv $H_2N{-}CH{=}NH$

Fig. (5)

As mentioned in the introduction, the objectives of this work are the synthesis and unambiguous characterisation of the 1,3-diaza[3.3.3]cyclazine (21) and pyrazino[2,1,6-*de*:5,4,3-*d'e'*]diquinolizine (20). Fig. (3) describes the formation of [1,2,4]-dithiazolo[3,4,5-*de*]-quinolizinium perchlorate (30) which, it was envisaged, would afford both of the target compounds by means of chemistry with good literature precedent [Figs. (4) and (5)]. These figures are repeated here for convenience.



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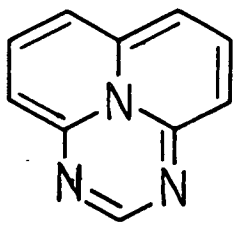
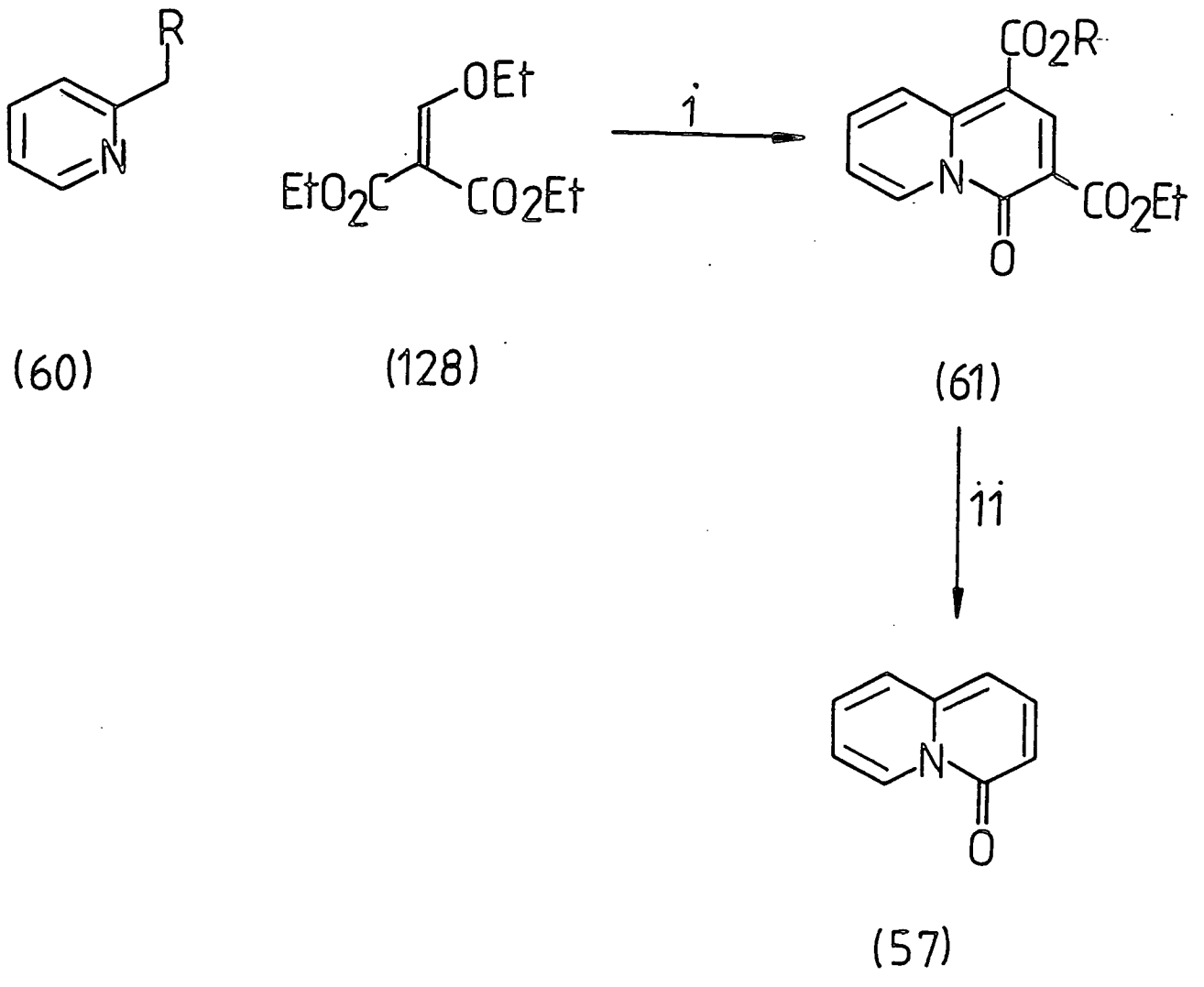


(21)

It was hoped that the successful synthesis would be easily adapted to introduce substitution into the parent molecules as this would affect both the molecular orbitals and redox potentials of the compounds and thus enhance their possible utility as donor molecules in the charge-transfer complexes present in organic conductors.



i $Na^{+}OEt^{-}$

ii 5M HCl

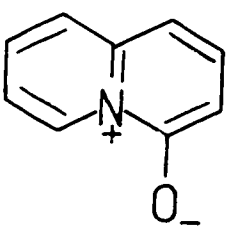
Fig.(28)

SYNTHESIS OF[1,2,4]-DITHIAZOLO[3,4,5-*de*]QUINOLIZINIUM PERCHLORATE (30)

This compound has been previously synthesised in these laboratories[15], but a brief description of the method will be included here in the light of some improvements to the original work.

Quinolizin-4-one (57) was readily synthesised according to the method of Smith[75] which afforded greater yields than the original procedure of Boekelheide[27]. Chilled ethanolic solutions of ethyl 2-pyridylacetate (60, R=CO_2Et) and diethyl ethoxymethylenemalonate (128) were added to sodium ethoxide at 0°C. Prolonged stirring followed by the addition of water led to the precipitation of 1,3-di(ethoxycarbonyl)quinolizin-4-one (61) in 83% yield. The ester groups were then removed simultaneously by refluxing in 5M HCl, yielding 80% of the parent quinolizin-4-one (57)[27] according to Fig. (28).

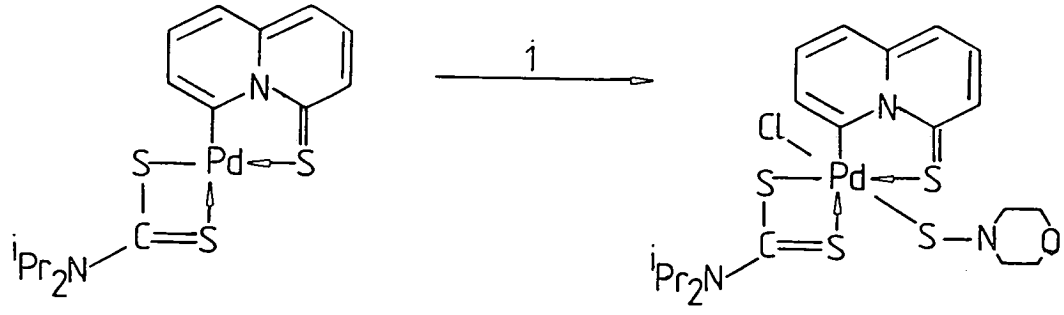
The 6-position of quinolizin-4-one is resistant to electrophilic substitution and, despite the contribution of the canonical form (58), it is not known to be susceptible to nucleophilic attack.



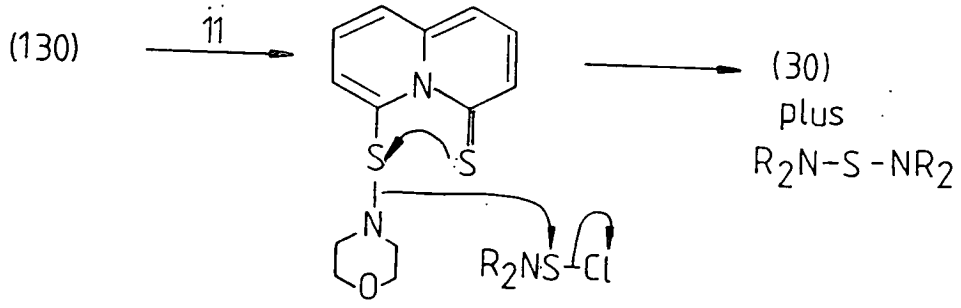
(58)

Accordingly, Davis[45] undertook to explore the possibility that cyclopalladation might provide a means of activating this position. However, oxygen donors are poor ligands for palladium, indeed there are no examples of cyclopalladated oxygen donor ligands. Thus the conversion of the carbonyl of (57) to a thiocarbonyl was deemed necessary as sulphur was known to be a suitable donor atom for palladium. Although Boekelheide[27] achieved this conversion using phosphorus pentasulphide, it was found to be more convenient to first convert quinolizin-4-one (57) into 4-chloroquinolizinium perchlorate (51, X-Cl) by reaction with phosphoryl chloride followed by perchloric acid. This salt was subsequently converted to the desired quinolizine-4-thione (29) by treatment with an aqueous solution of sodium sulphide as outlined in Fig. (29). All spectra obtained were in accordance with those reported.

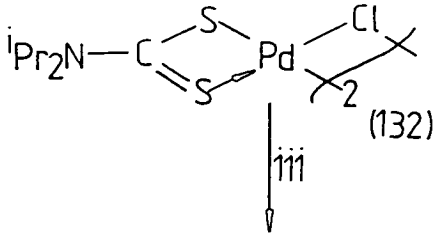
In the work of Davis[45], and subsequently Grinter[46], the cyclopalladation of (29) had proved irreproducible, but O'Neil[15] successfully effected the reaction by using more dilute solutions (*ca.* 0.015 mol dm^{-3}) than had these previous workers. In the present work, it was discovered additionally, that a slight molar excess of quinolizine-4-thione (29) was required in order to effect complete cyclopalladation. This observation served to support the cyclopalladation mechanism proposed by O'Neil [Fig. (16)], in which he suggested that the first step involves rapid sulphur-co-ordination of two quinolizine-4-



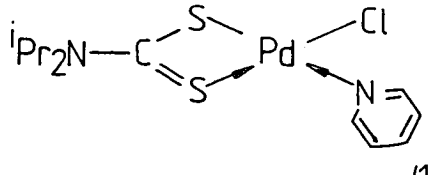
(32) (130)



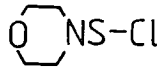
(131)
plus



(132)



(133)

i Oxidative Addition 

ii Reductive Elimination

iii Pyridine

Fig.(30)

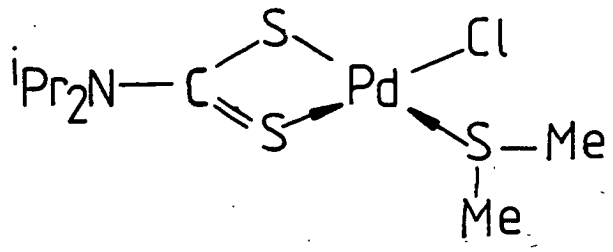
thione ligands to one palladium, inevitably requiring a small excess of the ligand.

Under optimised conditions of a five-hour reflux of dilute methanolic solutions of sodium tetrachloropalladate and quinolizine-4-thione in appropriate molar ratios, the chloride-bridged dimer (31) was obtained in high yield and identified by elemental analysis and comparison of the i.r. spectrum with that of O'Neil's product.

As mentioned previously, the insoluble, involatile dimeric compounds (31) are generally amenable to bridge-splitting reactions and the previous work[15,45,46] had shown that dithiocarbamate ions are the reagents of choice, leading to the monomeric species (32). Typically, molar equivalents of (31) and sodium diisopropyldithio-carbamate were stirred in dimethylformamide at room temperature for five hours and the concentrated reaction mixture purified by chromatography on alumina and recrystallised from benzene, yielding the desired dithiocarbamato complex (32) (86%) as verified by the accordance of all spectra with those reported[15].

As established by O'Neil, the most efficient method for thiodepalladation of compound (32) was the reaction with morpholine-N-sulphenyl chloride (129) according to the proposed mechanism of Fig. (30). Separation of the desired dithiazolium salt (30) from the insoluble chloride-bridged dimeric by-product (132) proved impossible by chromatography or preferential solvent

extraction[15]. It was eventually effected by splitting the chloride bridge of (132) with a monodentate ligand. Pyridine was chosen because its hardness and poor thiophilicity render it unlikely to react with the disulphide bond of (30) - a problem which had been envisaged with trialkylphosphines. Treatment of (132) with pyridine led to the soluble orange complex (133), allowing the insoluble dithiazolium salt (30) to be removed by filtration. It was found in this work that dimethyl sulphide effected this bridge-splitting reaction with equal efficiency, resulting, presumably, in the soluble orange complex (134), although its structure was never investigated, and once again allowing the dithiazolium salt (30) to be removed by filtration.

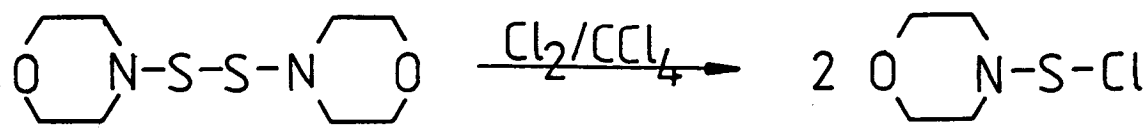


(134)

An alternative mode of separation of (30) and (132) was to add methanol to a mixture of the two compounds. The dithiazolium salt (30) dissolved but the dimeric by-product did not and could be removed by filtration. Concentration of the deep red filtrate thus obtained gave the desired product. However, yields of salt (30) were

lower, perhaps due to the sparing solubility of (30) in methanol.

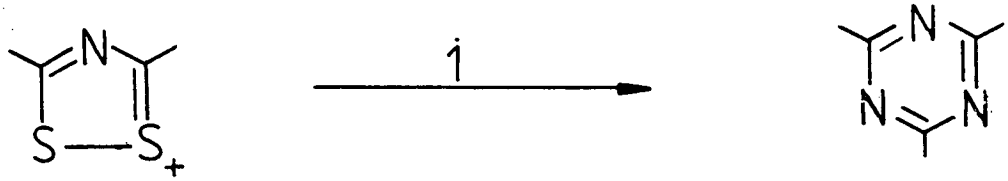
The synthesis of (30) was thus achieved by treating a solution of dimorpholinyl disulphide (135) in dichloromethane with a standardised solution of chlorine in carbon tetrachloride, generating morpholine-N-sulphenyl chloride (129) *in situ*. To this solution was added a solution of (32) in dichloromethane and the resulting precipitated mixture of (30) and (132) separated according to the aforementioned method. The chloride salt of (30) was generally converted to the perchlorate by treatment with perchloric acid. This *in situ* generation of morpholine-N-sulphenyl chloride afforded yields 8-10% in excess of those reported by O'Neil, whose method involved the isolation of the morpholine N-sulphenyl chloride.



(135) (129)

REACTIONS OF [1,2,4]DITHIAZOLO[3,4,5-*de*]QUINOLIZINIUM PERCHLORATE (30)

With this compound to hand, it was envisaged that nucleophilic attack at one of the carbon-sulphur bonds by an amidine, followed by subsequent elimination of both sulphur atoms would lead to the target molecule (21). This type of reaction is known to occur for 3,5-disubstituted 1,2,4-dithiazolium salts (103) leading to triazines (113)[48] Fig. (31).



(103) (113)

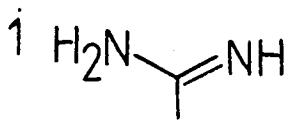
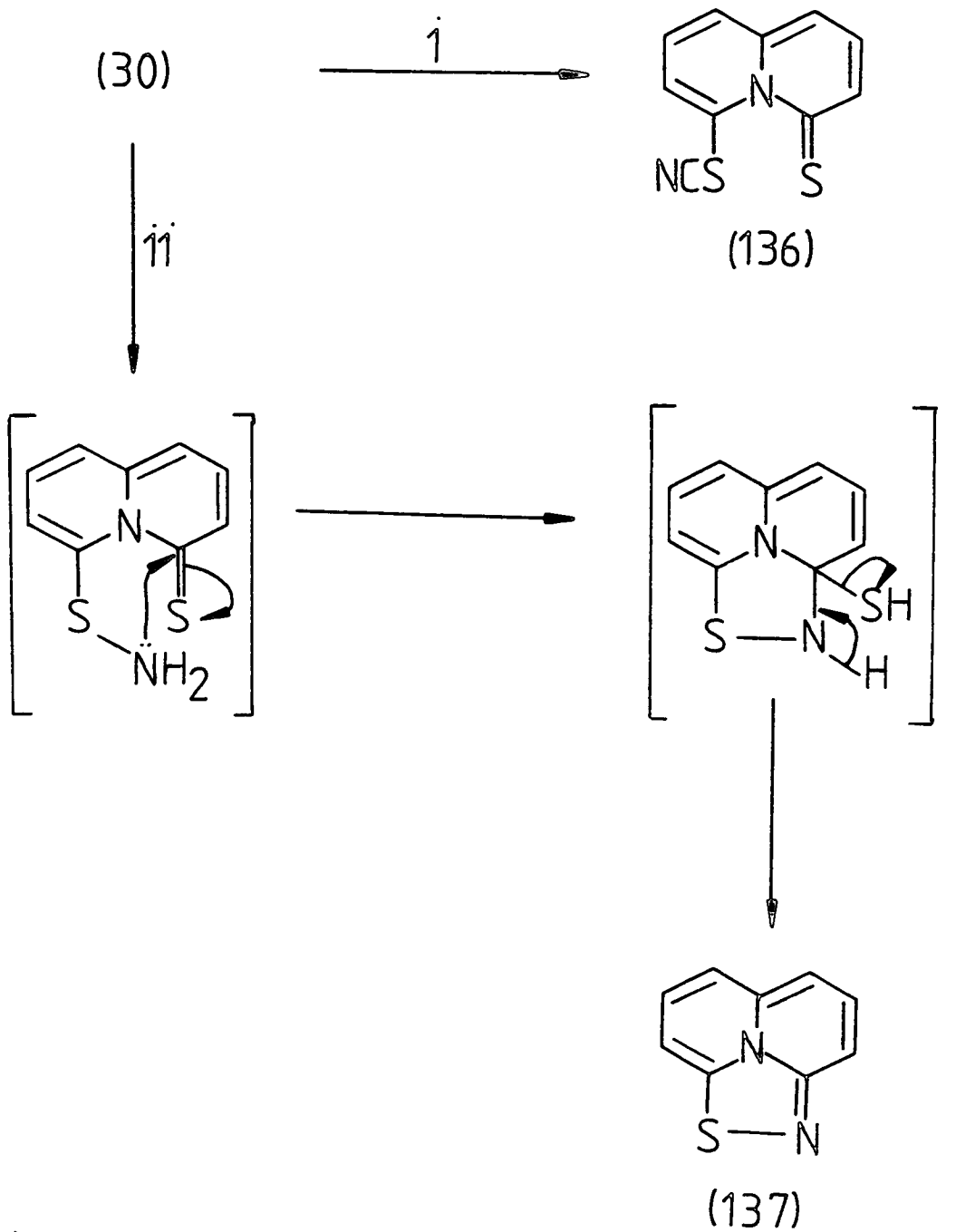


Fig. (31)

However, the dithiazolium system described here is one in which the nitrogen atom and the 3- and 5-substituents are part of the same fused ring and is thus far unreported in the literature. Its reaction with amidines or indeed any nucleophile therefore represents a new area of investigation.

O'Neil attempted the reaction of (30) by refluxing



i CN^-

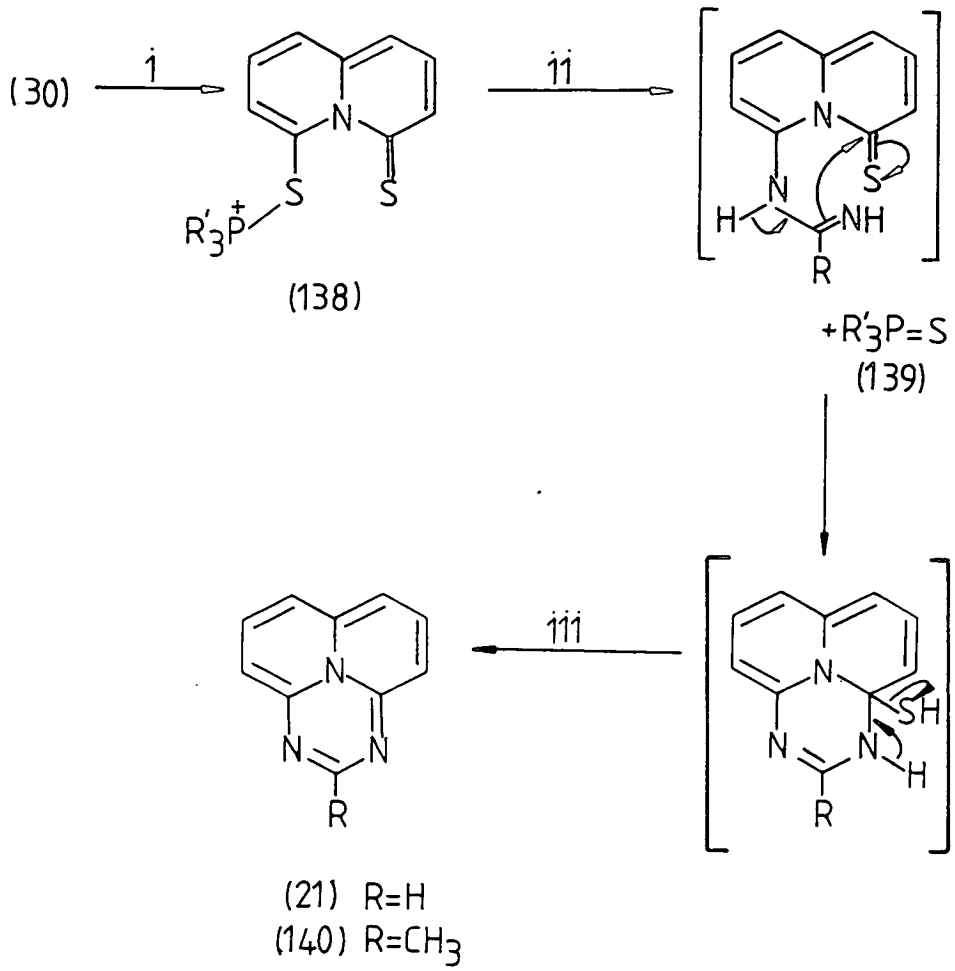
ii NH_3

Fig. (32)

with formamidine acetate in methanol and in 2-methoxyethanol but was unable to isolate any products. Heating the same two reagents in the absence of a solvent led to trace amounts of products tentatively formulated as (136) and (137) on the basis of their mass spectra. Formamidine is known to decompose around 100°C to ammonia and hydrogen cyanide[76], and these would be capable of nucleophilic attack on the quinolizinium nucleus according to Fig. (32).

In this work it was hoped that advantage could be taken of such a nucleophilic attack on the sulphur atom by the use of tri-*n*-butylphosphine[77] or trimethyl phosphite, well known disulphide bond-cleaving reagents. It was envisaged that the reaction would proceed [Fig. (33)] by initial attack of the phosphorus lone pair on one of the sulphur atoms to form (138) which would be susceptible to nucleophilic attack by the amidine at the carbon atom of the C-S bond, leading to elimination of the stable trialkylphosphine sulphide (139). Subsequent cyclisation and loss of hydrogen sulphide would afford the 1,3-diaza-[3.3.3]cyclazine (21) or (140).

In practice, molar equivalents of trimethyl phosphite and formamidine acetate were added to a solution of (30) in acetonitrile. The red colour of the solution darkened after 1h reflux under nitrogen but t.l.c. indicated that starting material remained. After addition of a further molar equivalent of each of the reagents and prolonged



i R'_3P

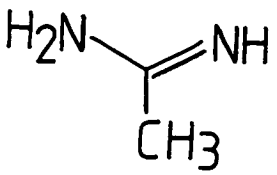
ii H_2N NH, R

iii $-H_2S$

Fig. (33)

heating, no starting material was evident. The recovered material was subjected to preparative t.l.c., but yielded only quinolizine-4-thione (29) (40%), identified by proton n.m.r. and mass spectrometry. The mode of formation of (29) could not be fully rationalised, although it is known that tervalent phosphorus compounds can often remove one sulphur atom from a disulphide[78]. None of the other reaction products evident in trace amounts on t.l.c. could be isolated.

The total lack of evidence for the participation of the formamidine moiety in nucleophilic attack led to the assumption that either a) the prolonged reflux at ~ 85°C was causing amidine decomposition or b) resonance delocalisation of the nitrogen lone pairs was reducing the nucleophilic character of the amidine below the threshold required for nucleophilic attack on the delocalised system of the dithiazolium ion (30). With these assumptions in mind, acetamidine (141) was used in a similar experiment in the hope that the methyl group would confer improved properties in both these categories.



(141)

One molar equivalent of tri-*n*-butylphosphine was added to a solution of (30) in acetonitrile. No colour change was apparent, however, t.l.c. indicated the formation of a yellow compound (Rf 0.82) and an orange compound (Rf 0.64). No attempt was made to isolate or identify these. Acetamidine hydrochloride and potassium carbonate were added and the mixture warmed for a prolonged period during which the solution became blue/green and t.l.c. indicated the presence of a similarly-coloured compound (Rf 0.14). After partial evaporation, the reaction mixture was subjected to preparative t.l.c., revealing ten narrow, intensely- coloured bands, the major one being that of the blue/green compound. The colour of this major component was encouraging in view of the fact that the radical cation of the parent [3.3.3]cyclazine (3) is known to be blue[6a]. Difficulty in removal of the blue colour from the silica seemed consistent with the existence of a charged species. However, hopes that the blue compound was the radical cation of the 1,3-diaza[3.3.3]cyclazine (140) were dispelled when treatment with the reducing agent sodium dithionite failed to alter the colour or effect its removal from the silica. This removal was eventually achieved using methanolic dichloromethane, but the only compound detectable by mass spectrometry was tri-*n*-butyl phosphine oxide (m/z 218). Although this may have been formed from the phosphine sulphide (139), no other evidence was obtained for the occurrence of the proposed

reaction [Fig. (33)].

In the light of the failure of the aforementioned methods, an alternative approach to molecule (21) was attempted [Fig. (5)].

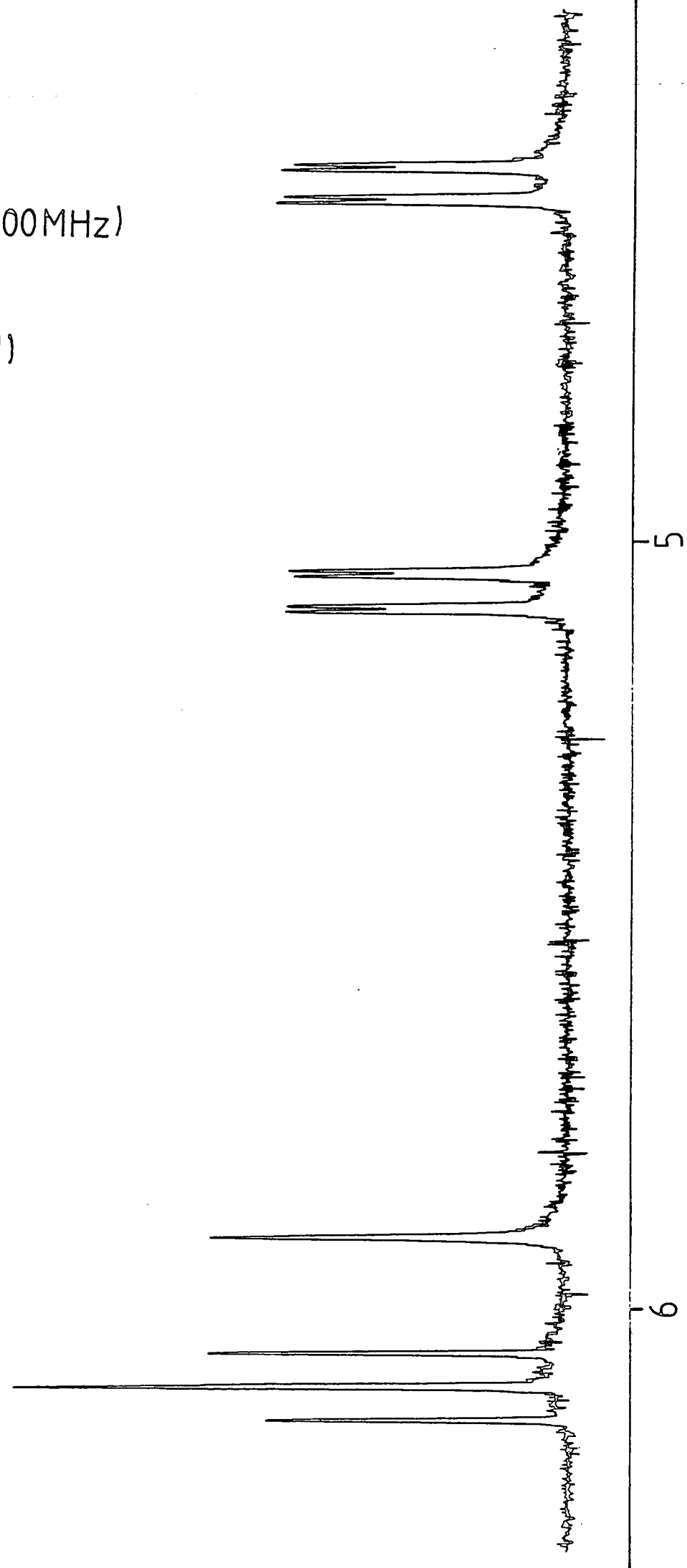
An aqueous solution of the dithiazolium salt (30) was treated with two molar equivalents of alkaline sodium dithionite at ice-bath temperature, causing the red solution to precipitate an orange/brown solid. Subsequent treatment with a molar equivalent of methyl iodide in dichloromethane caused dissolution of the precipitate and transferrence of most of the colour to the organic layer, which was removed and subjected to preparative t.l.c., affording the desired 6-methylthioquinolizine-4-thione (37) in low-moderate yields, as identified by proton n.m.r. at 360 MHz and accurate mass measurements, along with quinolizine-4-thione (29) in approximately equal yields.

The synthesis of 4,6 bis(methylthio)quinolizinium ion (38) was achieved by treating a warm solution of (37) in ether with an excess of methyl iodide. On cooling, the orange/red solution became lighter in colour with the concomitant precipitation of a yellow solid. Evaporation of the reaction mixture to dryness afforded (38) in 96% crude yield as verified by FAB mass spectrometry and accurate mass measurement. The crude reaction product was not purified due to lack of time and material, but was dissolved in acetonitrile and the yellow solution treated

^{1}H nmr (200MHz)

of

(21)



with an excess of formamidine acetate. Prolonged reflux under nitrogen led to the consumption of starting material and the formation of a blue material as observed by both t.l.c. and the green colour of the reaction mixture. When the reaction was complete, the green solution was concentrated and subjected to preparative t.l.c. eluting with dichloromethane/ethanol (5%). The blue band (Rf 0.60) yielded the desired 1,3-diaza[3.3.3]cyclazine in 95% yield as verified by the usual spectroscopic methods.

The ultraviolet spectrum of (21) showed four very low intensity absorptions at long wavelength (> 600 nm) each separated by ~*ca.* 70 nm. The short wavelength region exhibited two strong absorptions between 200 and 300 nm and one strong absorption with four shoulders between 300 and 400 nm. The relative intensities and positions of these signals were consistent with the values reported for other polyaza[3.3.3]cyclazines with a 1,3-arrangement of nitrogen atoms[79].

The proton n.m.r. spectrum exhibited a triplet of integral 2H at δ6.06 due to the β-protons, a singlet of integral 1H at δ5.88 due to H-2, and two doublets of doublets, each of integral 2H at δ5.10 and δ4.61 due to the α-protons. The shielding of the α-protons with respect to the β-protons is consistent with the localisation of electron density at these α-positions, as is seen in Fig. (1).

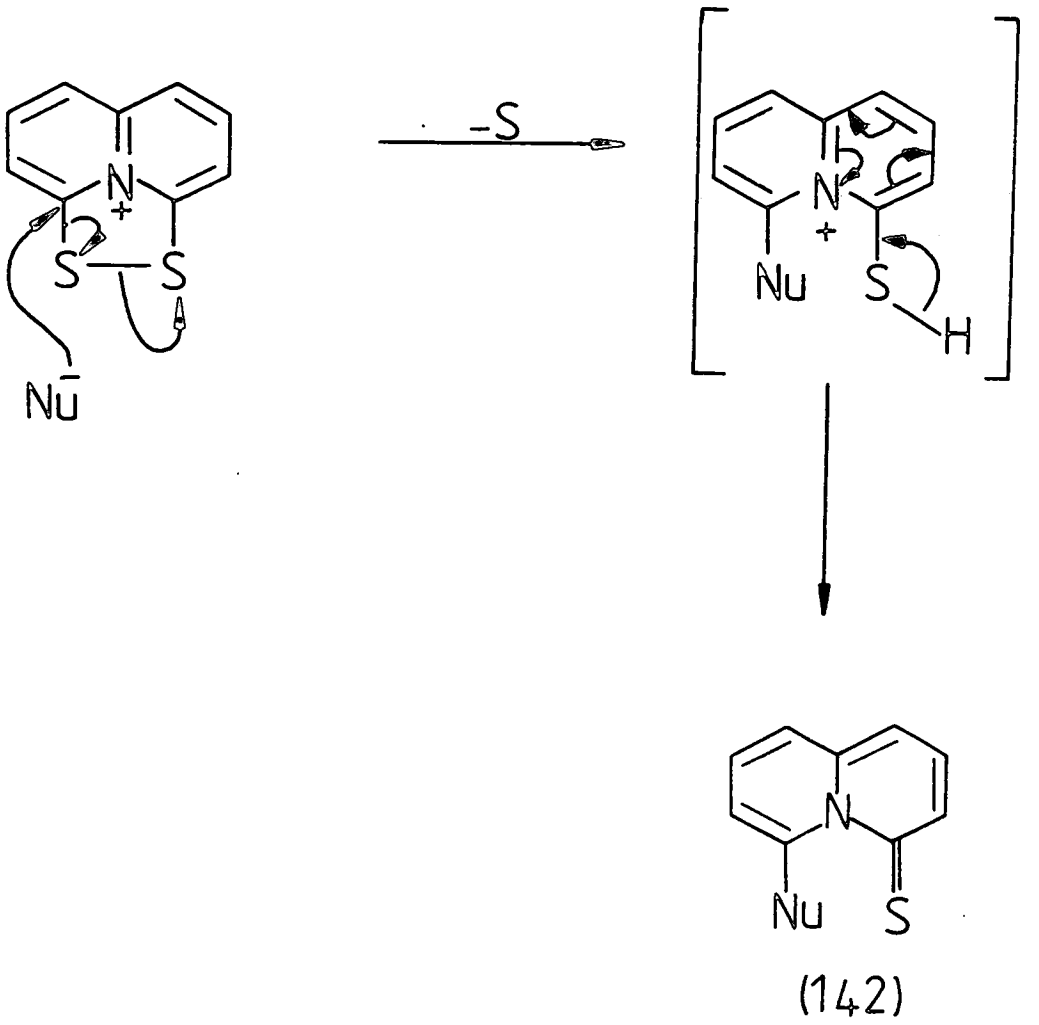
The relative position of the proton n.m.r. signals is

consistent with the trend observed by Matsuda and Gotou[14], that with increasing number of nitrogen atoms in the periphery, the proton n.m.r. signals occur at progressively higher frequency than those of the parent [3.3.3]cyclazine. The authors[14] found that the typical range of proton n.m.r. signals in the diaza[3.3.3]-cyclazine series was δ6.34 - δ3.90 and, as can be seen, the values obtained for (21) lie within this range.

Prior to this work, 1,3-diaza[3.3.3]cyclazine (21) was the only diaza[3.3.3]cyclazine whose synthesis had not been reported. This work, therefore, effects the completion of the diaza[3.3.3]cyclazine series.

The synthetic approach to (21), the parent of the 1,3-diaza series, could be easily extended to the synthesis of substituted analogues, e.g. the use of C-substituted amidines in the final step would result in 2-substituted analogues of (21). The introduction of substituents into other peripheral positions would, in theory, be feasible by the use of suitably-substituted dithiazolium cations (30) which, in turn, could be obtained from the corresponding quinolizine-4-thiones. However, the effect of the substituent(s) in such quinolizine-4-thiones upon the highly sensitive cyclopalladation and thiodepalladation steps would require careful study.

Unfortunately, lack of time prevented the investigation of the electrical properties of (21) or the

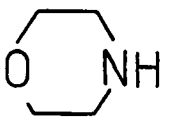


(142)

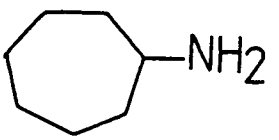
Fig. (34)

introduction of substitution into the parent.

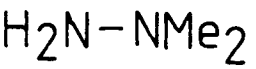
The general reactions of dithiazolium salts (103) with nucleophiles are covered in the introduction [Fig. (22)] and it was hoped in this work to investigate analogous reactions of (30) [Fig. (34)]. To this end, (30) in acetonitrile was treated with molar excesses of nucleophile and warmed under argon. The nucleophiles used were morpholine (143), cycloheptylamine (144), unsym-dimethylhydrazine (145), *p*-thiocresol (146) and methoxide ion.



(143)



(144)



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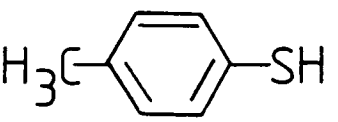
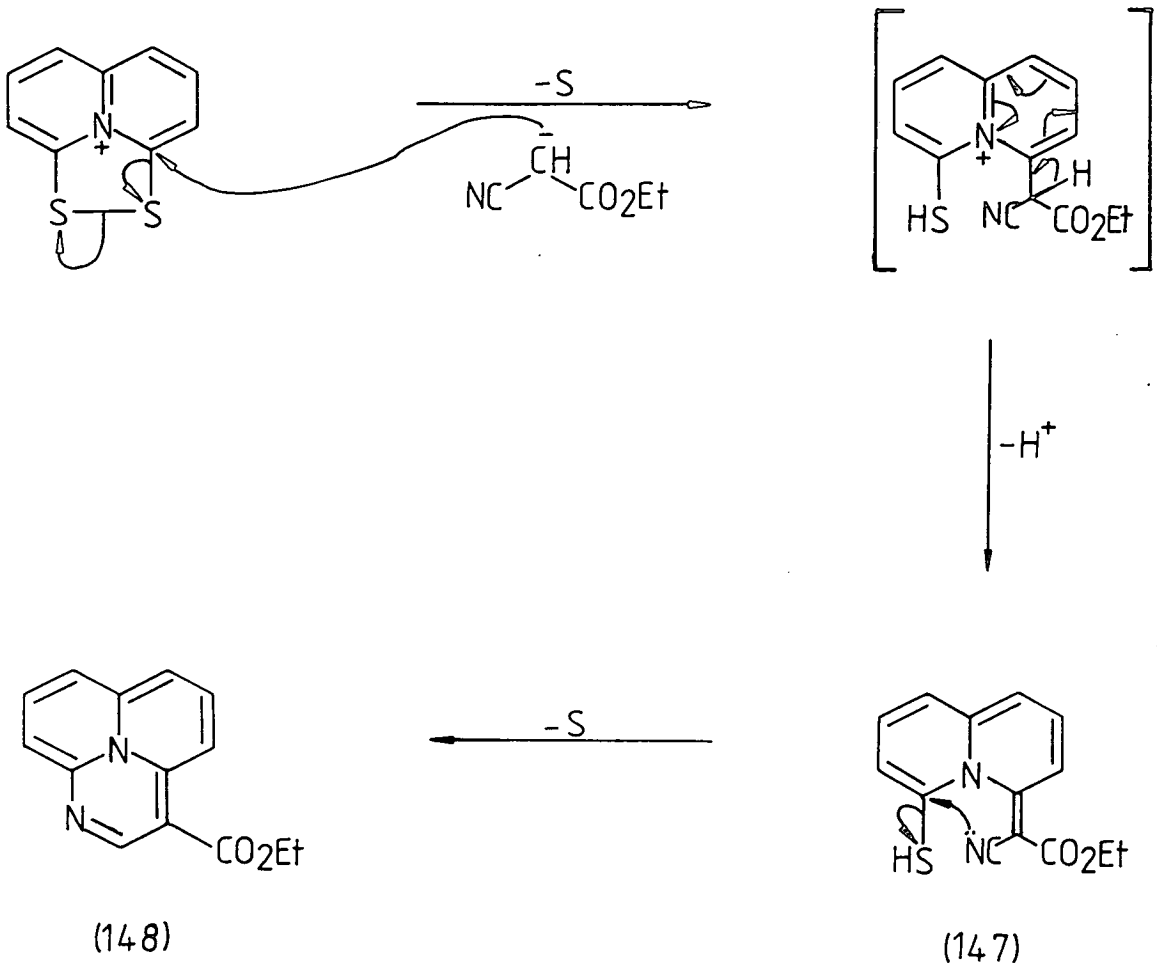


(146)

In each case, t.l.c. indicated the formation of a coloured material eluting close to the solvent front (in dichloromethane). However, attempts to isolate and characterise these materials failed. This may have been due to the air-sensitive nature of the products.

To further test the susceptibility of (30) to



(148) (147)

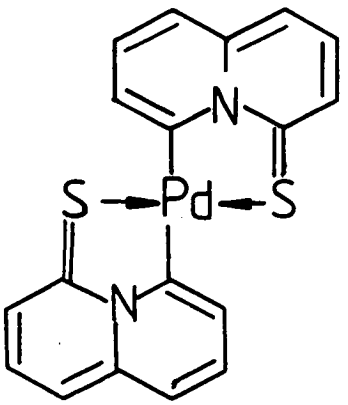
Fig. (35)

nucleophilic attack, a solution of the salt in acetonitrile was treated with a molar equivalent of ethyl cyanoacetate in the presence of sodium hydride, in the hope that a reaction of the sort outlined in Fig. (35) would occur. The resulting solution was warmed under argon until t.l.c. in dichloromethane indicated the formation of a fast-moving green material which was sensitive to air. Column chromatography under argon gave a fast-moving band which showed some evidence of partial separation into two components. The proton n.m.r. spectrum (sealed tube) of the material recovered from this band exhibited signals in the δ8.00-7.25 region and between δ6.25-4.80. The higher frequency signals were complicated and could not be assigned. However, the set of lower frequency signals could be interpreted as arising from two independent AMX systems (two overlapping triplets in the region δ6.25-5.95 and four partially overlapping doublets of doublets in the region δ5.51-4.73). This interpretation is consistent with the presence of a quinolizine substructure in which the two rings are non-equivalent and are linked to atoms other than H at positions 4 and 6. The strong shielding of all the proton signals in this region is comparable to that observed in the 1,3-diaza[3.3.3]cyclazine and suggests some degree of antiaromaticity which might be explained in terms of a tricyclic, cyclazine-like molecule in which positions 4,5 and 6 of the quinolizine substructure form part of another

fused ring. In the absence of further evidence, the possible nature of this third ring was purely a matter for speculation.

In an attempt to separate the two components of this material, the mixture was subjected to further silica column chromatography. Only trace amounts of separated materials were recovered. It was believed that decomposition had occurred on prolonged exposure to silica.

Repetition of the experiment led, on chromatographic separation, to a blue and a yellow material. The proton n.m.r. spectrum of the yellow material did not correspond with either of the regions of the mixed sample obtained in the previous experiment. Its mass spectrum exhibited peaks at m/z 426 (Pd isotope pattern), 160 (quinolizine-4-thione) and it was thought to be (149) formed as a result of some palladium-containing residues remaining in the sample of (30). However, comparison of the proton n.m.r. spectrum with an authentic showed, in general, poor correlation, but the possibility of (149) present along with a larger amount of a yellow material of aromatic character which could not be further identified because of its sensitivity to air.



(149)

The proton n.m.r. spectrum of the blue material was weak due to its limited solubility in duteriochloroform, but exhibited no signals corresponding to those in the mixed sample from the previous experiment. The mass spectrum of this compound offered no evidence for the existence of any of the compounds from the expected nucleophilic attack.

The irreproducibility of the original, promising, reaction led to the belief that a number of reactions were in competition and that the outcome of the reaction was very sensitive to the conditions employed. In the hope of reducing the number of competing reactions, an analogous experiment to the original was conducted on diethyl malonate. Treatment of (30) with a molar equivalent of diethyl malonate under argon in the presence of sodium hydride led to the formation of an orange/brown precipitate which was removed by filtration. Its mass

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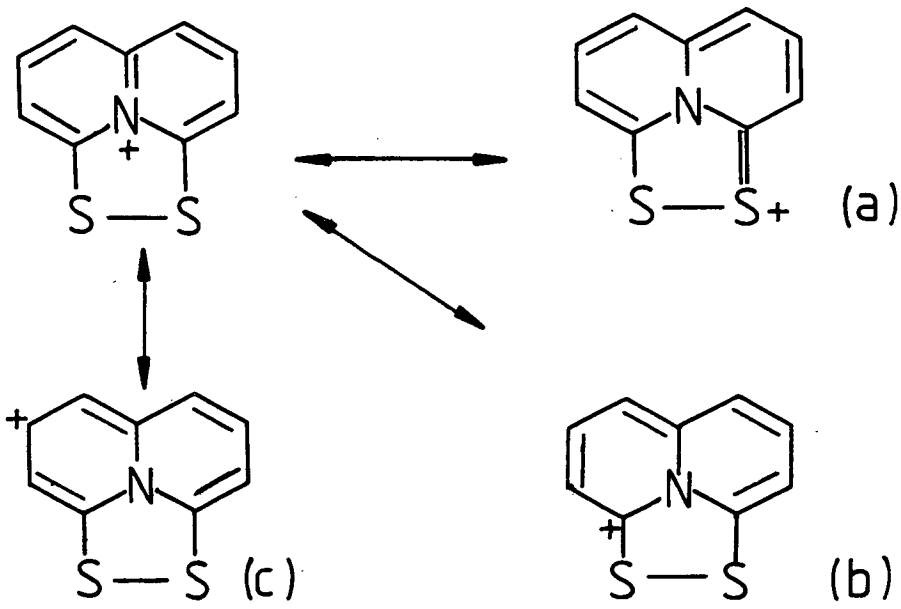
spectrum exhibited peaks at m/z 426 and 160 - consistent with the formation of (149). However, its proton n.m.r. spectrum was not consistent with this compound and the solid remained unidentified. The filtrate, on concentration, yielded a solid whose proton n.m.r. showed signals in two distinct regions - δ8.25-7.25 and δ5.95-4.95. However, its sensitivity to air prevented separation of these two components or further elucidation of their identity.

In retrospect, the formation of trace amounts of (149) may have been due to the reaction of excess hydride ion (sodium hydride was supplied as a 50% suspension in mineral oil) on the dithiazolium salt (30) to form quinolizine-4- thione, which in the presence of trace amounts of palladium-containing impurity in the sample of (30) may have formed (149). The use of an alternative base might have eliminated this problem. However, lack of time prevented investigation of this possibility and indeed the investigation of other experimental factors to which reaction of (30) is evidently highly sensitive. The choice of acetonitrile as a solvent may, in retrospect, have been a poor one and its possible participation in competing reactions cannot be ruled out at this stage. In the light of the unpredictability and irreproducibility of reactions between (30) and nucleophiles, it is obvious that the reactivity of (30) is not directly analogous to that of monocyclic dithiazolium

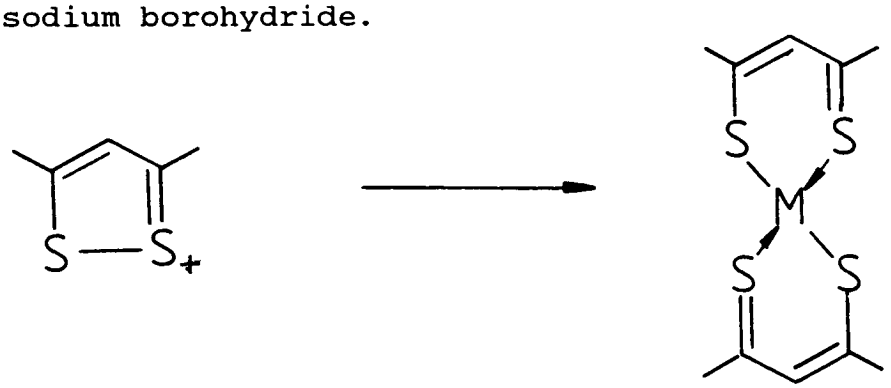
salts. This may be due, in part, to the possibility of nucleophilic attack at positions other than C-4 due to the canonical forms (30a and c). It is therefore obvious that a detailed study of the reactivity of dithiazolium salt (30) towards nucleophiles is necessary before it can be used with confidence in reactions of the type attempted here. Such a study was outwith the scope of this work.



The reaction of 1,2-dithiolium salts (150) with nucleophilic reagents such as hydroxide ion, hydrosulphide ion and ammonia in the presence of metal ions, namely Ni(II) and Cu(II) has been reported[80]. In a similar manner, reduction of compounds (150) by borohydride or

dithionite in the presence of metal ions[83] readily yields complexes of the type (151) as shown in Fig. (36).

As mentioned in the introduction, 1,2,4-dithiazolium salts (103), when treated with thiols tend to form dimers of the type (119) or complexes (120) when a divalent metal is present [Fig. (26)]. These latter complexes would be of great interest in this work, but in view of the unsuccessful reaction of (30) with a thiol [*p*-thiocresol (146)] their synthesis was attempted using the reducing agent sodium borohydride.



(150) (151)

Fig.(36)

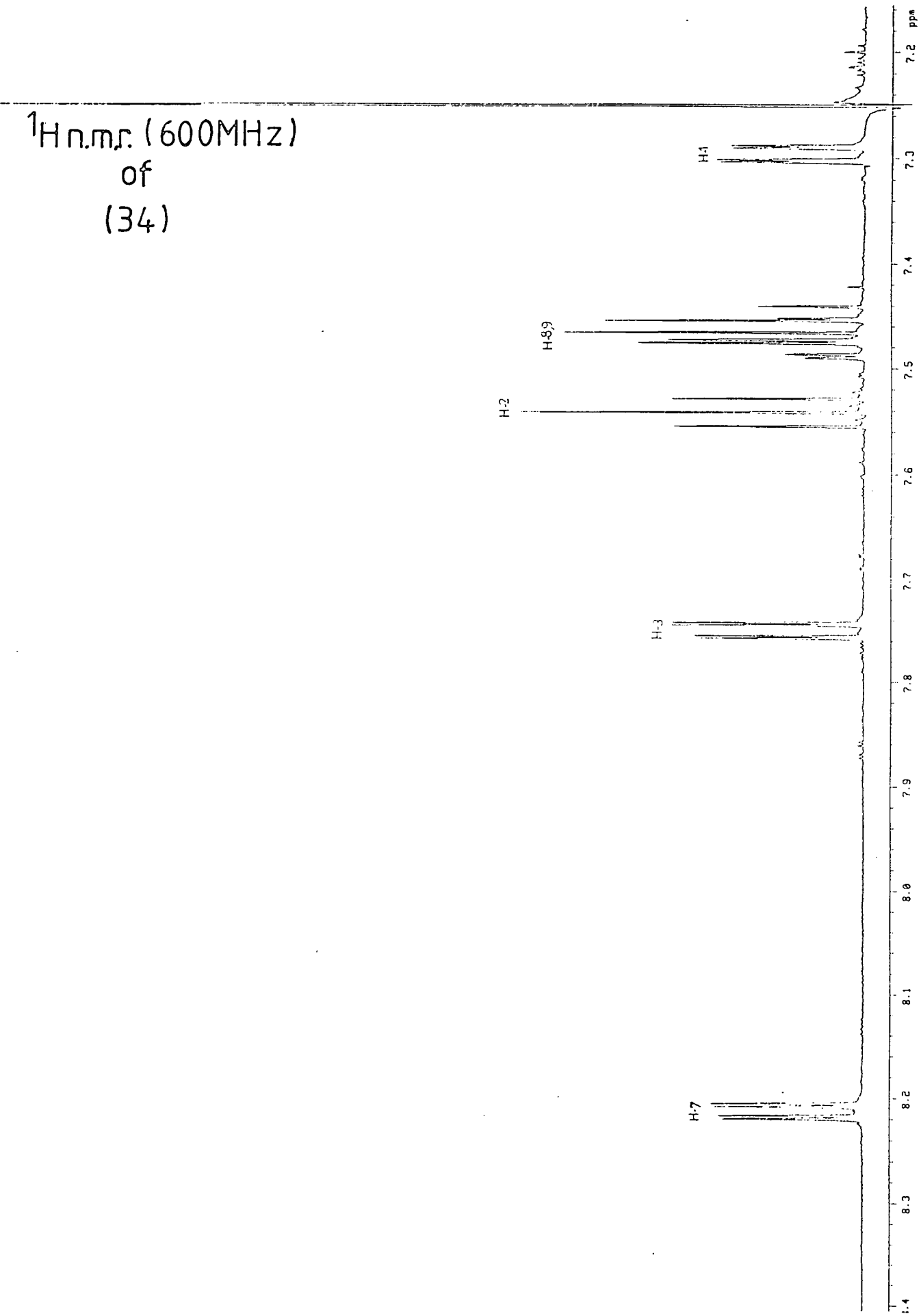
In the first instance, an aqueous solution of (30) was treated with sodium borohydride followed by methanolic sodium tetrachloropalladate solution with the exclusion of air. The resultant finely divided red/brown solid was separated from the solution by centrifuge and dried *in vacuo*. It was sparingly soluble in most organic solvents including DMSO and gave a t.l.c. with four spots. Soxhlet extraction into dichloromethane gave an orange solid,

which when subjected to mass spectrometry gave a molecular ion peak at m/z 426 - inconsistent with the predicted complex (152) of mass 490. However, the presence of a molecular sulphur peak (m/z 256) and its typical fragment peaks (m/z 224 etc.), led to the proposal that heating the sample in the mass spectrometer ion source had caused extrusion of two sulphur atoms from (152) to form (149) as indicated in Fig. (37).

In an attempt to effect this extrusion on a preparative scale, the solid (152) was sublimed at 170°C/ 0.8 mm, but examination of the sublimate indicated extensive decomposition to quinolizine-4-thione (29), and the residue had become charred.

The reaction was repeated using nickel (II) chloride as the source of the divalent metal and the analogous nickel complex (33) was obtained in high yield. The mass spectrum of a crude sample of (33) suggested the presence of trace amounts of (149) implying the existence of some palladium impurity in the sample of dithiazolium perchlorate starting material (30) - a point mentioned earlier in the discussion. The spectrum also suggested the occurrence of a sulphur extrusion reaction analogous to that observed in the mass spectrum of (152). In the case of the nickel complex, however, this extrusion reaction could be effected on a preparative scale by heating at 190°C/0.11 mm. Subsequent preparative t.l.c. of the residue yielded the doubly-cyclonickellated complex

^{1}H n.m.r. (600MHz)
of
(34)



(34) as a red solid. In addition, some quinolizine-4-thione (29) was observed along with a fast-moving yellow compound whose mass spectrum showed peaks at m/z 394 and 410 - consistent with the incorporation of one and two oxygen atoms respectively into the structure (34). The exact site of their incorporation remained undetermined.

On repetition of this experiment it was found to be more convenient to effect the sulphur extrusion in boiling *o*-dichlorobenzene and, after evaporation, to purify the residual solid by Soxhlet extraction into chloroform. This procedure was preferable to preparative t.l.c. because the desired complex (34) when adsorbed on silica was sensitive to aerial exposure, leading to the formation of the oxygenated compound (m/z 410). The more prolonged the period of exposure to these conditions, the greater the proportion of conversion.

Accurate mass measurement of the red solid was in accordance with the formation of (34). Analysis by proton n.m.r. at 600 MHz revealed the splitting pattern expected of two independent three-spin systems (one ABX and one AMX). Four doublets of doublets each exhibiting one large *(ortho)* and one small *(meta)* splitting were observed for protons 1,3,7 and 9. The doublet of doublets at δ8.21 was assigned to H-7, however, coupling constants to protons 8 and 9 could not be determined due to second order effects. The signal due to proton 9 occurred at δ7.48 and exhibited a coupling constant to proton 8 of 8.30 Hz. The signal

due to proton 8 appeared as a doublet of doublets (two large *ortho* couplings) at δ7.45 and $J_{8,9}$ was calculated as 8.30 Hz, but second order effects prevented further assignments for this ABX ring. The second ring exhibited an AMX splitting pattern with no second order effects, allowing complete assignment (see experimental).

With compound (34) available readily and in high yield from (30) it was hoped that its treatment with a powerful oxidising agent would effect the coupling reaction shown in Fig. (4) to produce (35), based on a report by Tsou and Kochi[81], who observed that square planar organonickel(II) complexes undergo reductive coupling of alkyl or aryl ligands in the presence of oxidants such as Br_2, I_2, Na_2IrCl_6, or Co(III), Tl(III) or Ce(IV) trifluoracetates in high yields.

Thus a solution of (34) in chloroform was treated with cobalt tris(trifluoroacetate) synthesised according to the method of Tang and Kochi[82]. The red solution became pale yellow/orange after stirring for 5 min. at room temperature and t.l.c. indicated complete consumption of starting material. The reaction mixture was filtered and the collected solid dried *in vacuo* and analysed by mass spectrometry. Peaks at m/z 378 (Ni isotope pattern), 160 and 117 were consistent with the existence of starting material, but contradictory to the t.l.c. observation. It was therefore tentatively suggested that oxidation of the complex to Ni(III) had occurred, but the desired coupling

reaction had failed.

The filtrate obtained in this reaction was concentrated to give a small amount of an orange material which was subjected to preparative t.l.c. The only identifiable compounds thus obtained were traces of quinolizine-4-thione (29) and elemental sulphur (m/z 256) suggesting that a small amount of decomposition had accompanied the aforementioned oxidation.

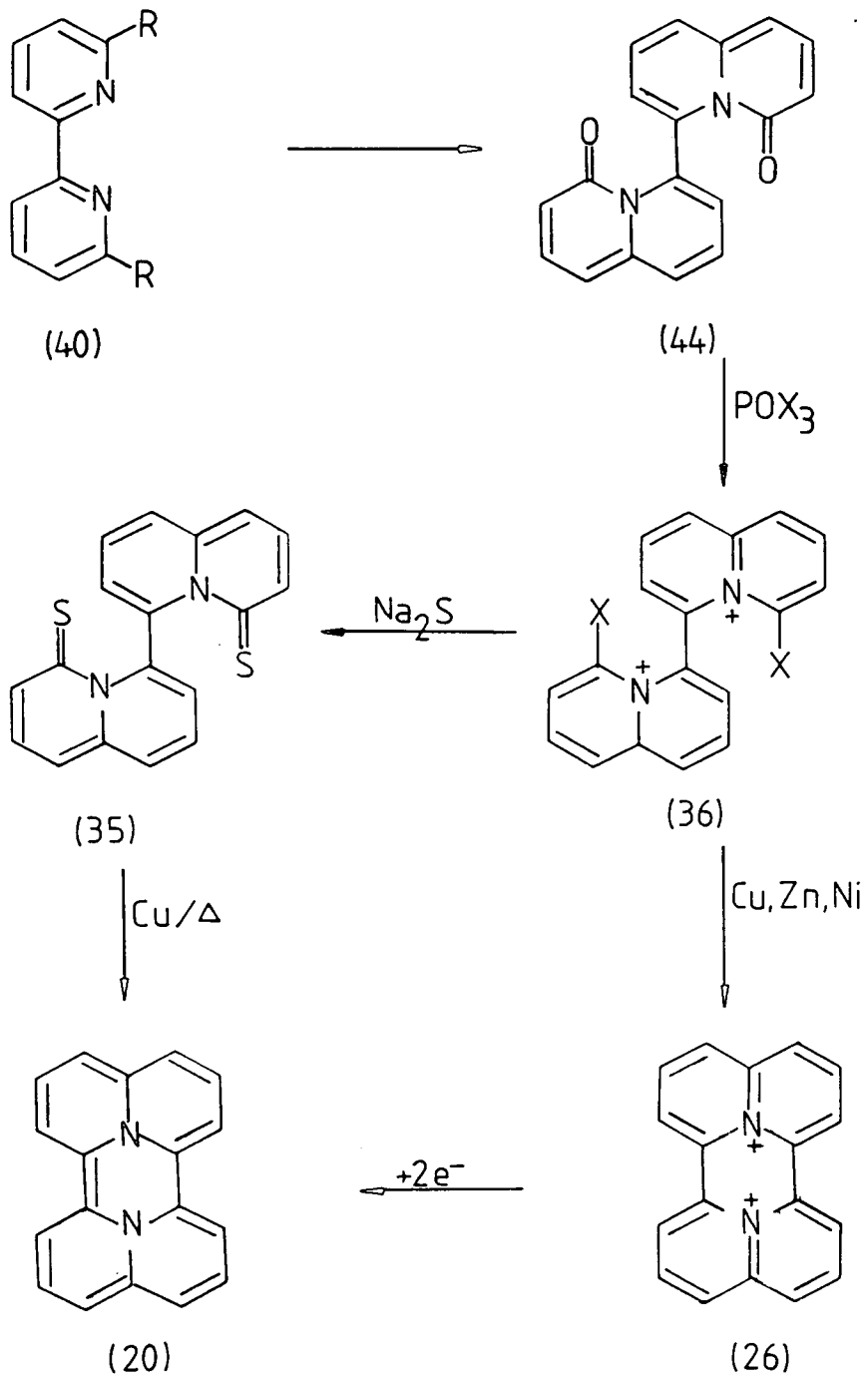

R
N
N
R
(40)
N
O
N
O
(44)
POX3
N
S
N
S
(35)
Na2S
N
+
X
N
+
X
(36)
Cu/Δ
Cu, Zn, Ni
N
N
(20)
+2e⁻
N
+
N
+
(26)

Fig. (38)

THE BIPYRIDINE APPROACH TO THE [18]-ANNULENE SYSTEM (20)

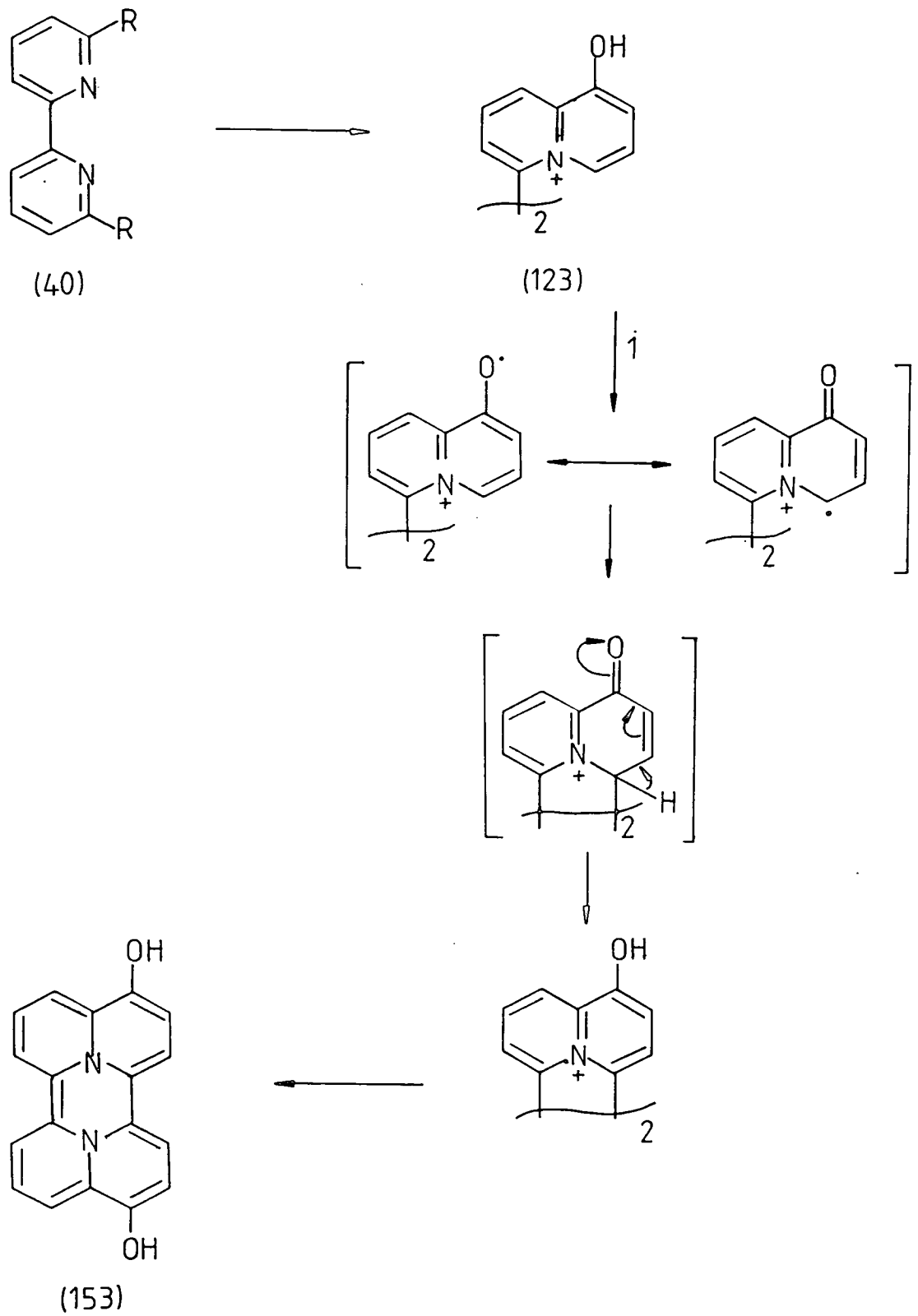
The work covered in this section describes synthetic routes to the target [18]-annulene system (20) using 6,6'-disubstituted-2,2'-bipyridines (40) as starting materials. It was envisaged that if molecules such as 6,6'-bis-(quinolizin-4-one) (44) or the 6,6'-bis-(1-hydroxy-quinolizinium)ion (123) could be synthesised, their conversion to (20) or its derivatives could be achieved according to Figs. (38) and (39) respectively. Thus the synthesis of (44) and/or (123) were our initial objectives.

Synthetic routes to quinolizin-4-one (57) and the 1-hydroxyquinolizinium ion (50) are known - as mentioned in the introduction and it was hoped in this work to utilise analogous ring-building approaches for suitably functionalised bipyridine starting materials.

There are no symmetrical 6,6'-disubstituted-2,2'-bipyridines commercially available and so the first part of this discussion is concerned with the synthesis of such compounds.

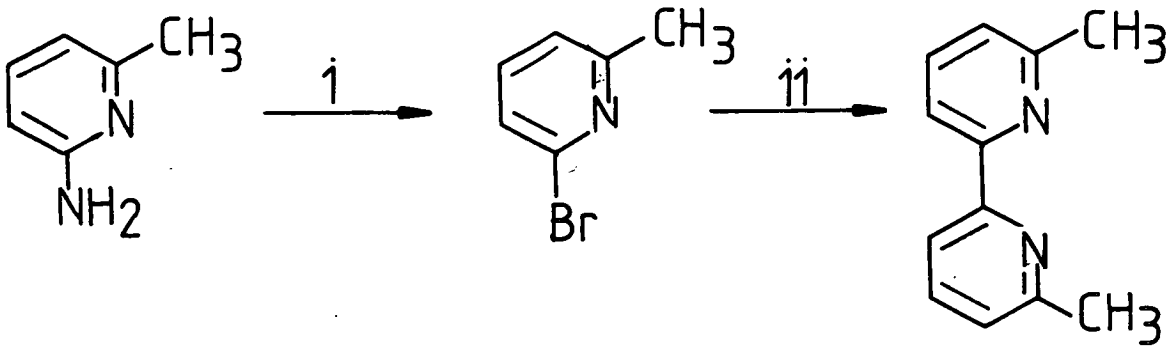
The Synthesis of 6,6'-Dimethyl-2,2'Bipyridine (41)

This compound had been previously synthesised by Newkome and co-workers[65] in 45% overall yield from 6-amino-2-picoline (154) according to Fig. (40).



i $K_3Fe(CN)_6$, PbO_2 , Ce^{IV}

Fig (39)



(154) (155) (41)

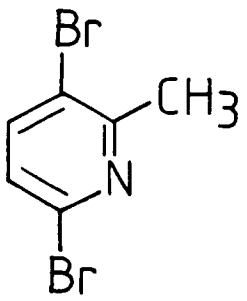
i $HBr, Br_2, NaNO_2$

ii $NaHCO_2, C_6H_6, Pd\text{-}C, PTC$

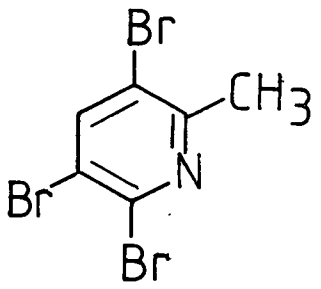
Fig. (40)

However, in this work, such yields could not be attained as the following discussion describes.

Synthesis of 6-bromo-2-picoline (155) in this work and that of Newkome was effected according to the Craig procedure[84]. Treatment of 6-amino-2-picoline (154) with 48% hydrobromic acid and bromine followed by sodium nitrite afforded the desired (155) along with di- and tri-bromo picolines as identified by proton n.m.r. of the crude reaction mixture. The dibromo-2-picoline (156) partially crystallised and could be almost completely removed from the mixture by filtration. Careful distillation of the remaining liquid resulted in removal of the tri-bromo compound (157) as established by the disappearance of two singlets at δ2.43 (CH_3) and δ7.87 in the proton n.m.r. spectrum of the distillate.



(156)



(157)

Complete removal of the dibromo by-product from the mono-bromo was effected by a second distillation and verified by n.m.r., i.e. the distillate showed a proton spectrum lacking in a singlet and two doublets at δ2.50 (CH_3), 7.19 and 7.60 respectively. Thus the desired 6-bromo-2-picoline was obtained in 44% yield and free from the poly-brominated by-products, exhibiting an n.m.r. spectrum consistent with structure (155), namely a singlet (CH_3), two doublets and a triplet. On expansion, both the doublets exhibited further coupling to each other and to the methyl protons. The spectrum of the dibromo compound exhibited similar long-range couplings, both of the doublets being further split into quartets. The structure of this dibromo by-product was established as (156) by means of an N.O.E. experiment. Irradiation of the methyl signal had no effect on the other signals, implying neither proton was in close proximity to the methyl group.

A possible explanation for the occurrence of poly-bromination may lie in the mechanism of the reaction. If

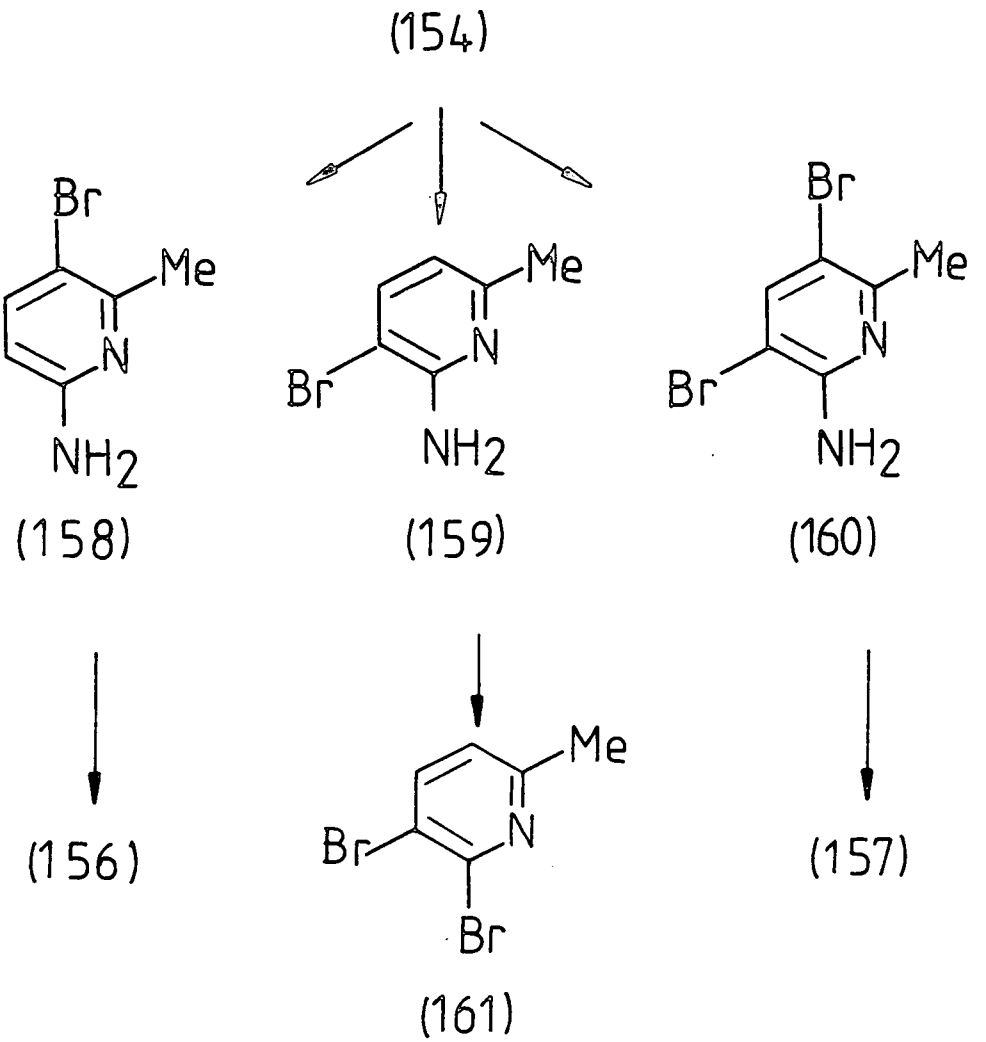
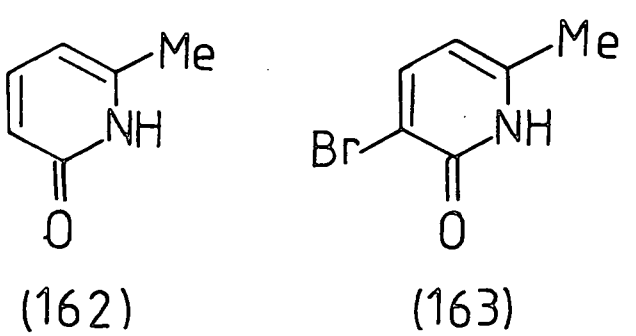

(154)
Br
Me
N
NH2
(158)
Me
Br
N
NH2
(159)
Br
Me
Br
N
NH2
(160)
(156)
Me
Br
N
Br
(161)
(157)

Fig.(41)


Me
NH
O
(162)
Me
Br
NH
O
(163)

electrophilic bromination occurred before the loss of the 6-amino function, then the result would be 3- or 5- bromo or 3,5-dibromo-6-amino-2-picoline (158-160) due to the *o/p*-directing effect of the amino group. Subsequent replacement of the amino function by bromine would result in 3,6- or 5,6-dibromo- or 3,5,6-tri-bromo-2-picoline (156, 161, 157) [Fig. (41)].

With a view to minimising this electrophilic attack, a number of repetitions of the original experiment were attempted wherein the addition of liquid bromine was done much more rapidly in an attempt to reduce the contact time of (154) and bromine. However, although this appeared to eliminate the formation of the tri-bromo compound, the dibromo was still produced in substantial proportions.

It should be noted that no mention of poly-brominated by-products is made in Newkome's report[65].

A further attempt to effect the desired conversion used a method based on the Sandmeyer reaction. Copper(I) bromide was therefore used instead of elemental bromine and was present in the solution during addition of sodium nitrite. However, this reaction only yielded 6-methyl-2-pyridone (162) and its 3-bromo analogue (163) as identified by proton n.m.r. and mass spectrometry.

The difficulties involved in the single-step replacement of the amino group by bromine prompted the use of a two-stage process *via* the pyridone (162). The conversion of 6-amino-2-picoline (154) to (162) was

carried out according to the method of Adams and Schrecker[85] using concentrated sulphuric acid and sodium nitrite followed by treatment with water, affording the off-white solid (162) in 88% yield. The second stage, i.e. conversion of (162) to (155), involved treatment of the former with phosphoryl bromide[86] at 170°C for six hours and effected a 43% conversion.

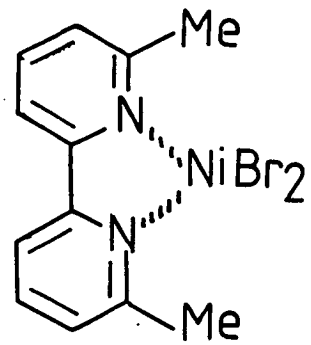
Despite the lower yield *via* this latter two-stage process [38% from (154)] the product was more easily purified than was that obtained by the method of Craig[84] [44% from (154)].

Conversion of the 6-bromo-2-picoline (155) to 6,6′-dimethyl-2,2′-bipyridine (41) was achieved in 50% yield by Newkome[65]. In the present work, the use of identical conditions yielded a maximum of 32%, i.e. maximum overall yield from (154) of 14%. This was initially believed to be due to the presence of di- and tri-bromo picoline contamination in early samples of (155). However, repetition of the conditions using the pure samples of (155) as obtained *via* the two-stage process[85,86] resulted in only 6% crude yield of the desired (41).

This rather surprising result led to the tentative assumption that these impurities perhaps affected the palladium catalyst in some advantageous manner.

In the light of the low yields of the above method the recently reported synthesis of (41) in 65% yield using a degassed Raney nickel catalyst[87] offered a promising

alternative. The method involved the treatment of 6-bromo-2-picoline (155) with a stoichiometric amount of thoroughly dried and degassed Raney nickel in refluxing toluene, yielding 6,6'-dimethyl-2,2'-bipyridine as its nickel bromide complex (164). Subsequent hydrolysis with water, extraction into chloroform and recrystallation from ligroin resulted in (41). However, despite careful attention to detail and rigorous exclusion of water and air, the maximum yield obtained in our hands was 22% of crude material.



(164)

In 1984, Tiecco and Testaferri[88] reported a simple and high-yielding method for the synthesis of bipyridines involving the coupling of halopyridines mediated by nickel phosphine complexes. Based on the method[89] for the coupling of aryl halides using Ni(0) complexes, the method utilised nickel tetrakis(triphenylphosphine) generated *in situ*[90]. Although the reaction was not reported for 6-bromo-2-picoline (155), the examples cited and their comparison with other literature procedures appeared

encouraging. However, in our hands, this method afforded a maximum yield of 16% of the target (41).

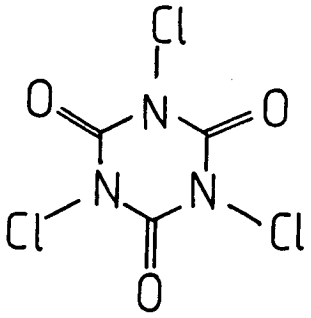
As described in the introduction, the synthesis of substituted bipyridines by reaction of a suitably-substituted pyridine with its corresponding N-oxide in the presence of a mixed palladium/platinum catalyst gave product yields in the region of 40%[64,66]. However, for the 2-picoline/2-picoline-N-oxide system the yield was only 18%. In this work a maximum yield of 10% was attained in the absence of platinum and no improvement upon this could be effected by prolonged reaction times nor the use of more active catalysts. This approach, therefore, offered no advantages over those previously described.

Attempted Synthesis of 6,6'-Bis(chloromethyl)-2,2'-Bipyridine (42)

As detailed in Fig. (7) it was envisaged that 6,6'-dimethyl-2,2'-bipyridine (41) could be converted to (42) by reaction with N-chlorosuccinimide as reported by Newkome[64]. However, in this work, yields were optimally 38% (un-isolated) and unreacted starting material (21%) was recovered. Newkome reported difficulties in isolating the product, losing around 30% in the process.

The low yields and isolation difficulties prompted the use of trichloroisocyanuric acid (165) as described by Jeromin[91] to effect the conversion of 2-picoline to

2-chloromethylpyridine (166).



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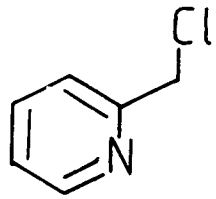


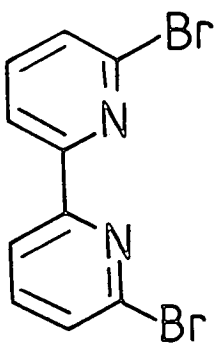
(166)

In accordance with the described method, a chloroform solution of 6,6′-dimethyl-2,2′-bipyridine (41) was refluxed with benzamide prior to addition of an excess of (165) but starting material was returned in almost quantitative yield. Trace amounts of the desired compound (42) were present, as established by n.m.r. (methylene protons at δ4.73) but prolonged reaction times and a greater excess of (165) failed to improve the yield of (42).

In view of the disappointingly low yields of the described reactions of Fig. (7), alternative approaches to the target (20) were sought, thus requiring more accessible bipyridine starting materials. The following discussion deals with the synthesis of such compounds.

The Synthesis of 6,6′-Dibromo-2,2′-Bipyridine (167)

This was achieved according to the method of Parks *et al*[70] in yields equivalent to or greater than those reported. Product identification was by proton n.m.r.,



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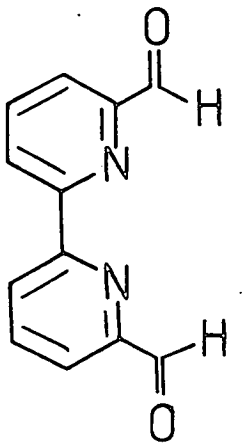

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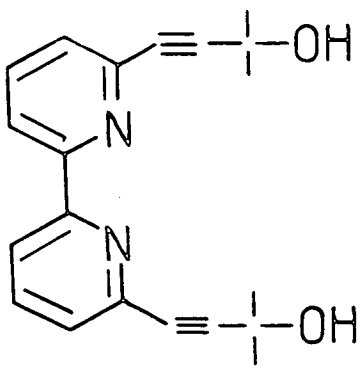
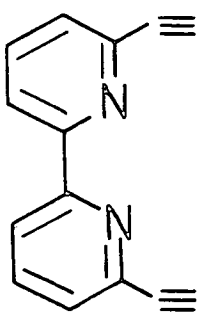


(171)



(169)

infra red and mass spectrometry. Compound (167) was found to be of considerable utility in the synthesis of other 6,6'-disubstituted-2,2'-bipyridines as the following description indicates.

The Synthesis of 6,6'-Diformyl-2,2'-Bipyridine (168)

Treatment of (167) with two molar equivalents of *n*-butyl-lithium followed by N,N-dimethylformamide according to ref. 70 led to the formation of (168) in 60% yield. All spectroscopic and analytical data were in accordance with those reported.

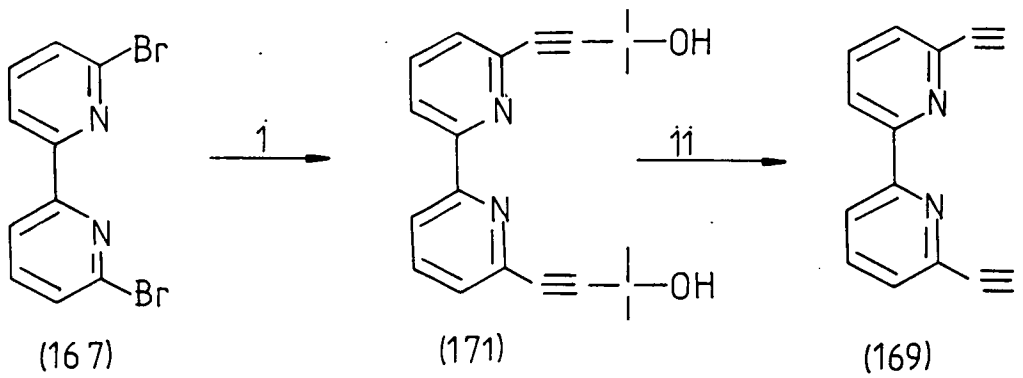
The Synthesis of 6,6'-Diethynyl-2,2'-Bipyridine (169)

A convenient synthesis of ethynyl-N-heteroarenes from the corresponding bromo-N-heteroarenes[92] led to the proposal that (167) could be converted to (169) by an analogous treatment.

A slight molar excess of 2-methyl-but-3-yn-2-ol (170) was added to a stirred solution of (167) in diethylamine containing a small proportion of benzene to aid dissolution of (167). The subsequent addition of a catalytic amount of bis(triphenylphosphine)palladium(II)-dichloride and copper(I)iodide with stirring at ambient temperature for 1-2h yielded 93% of (171) as a white solid mpt 156-158°C, exhibiting proton n.m.r., infra red and mass spectra and analysis in accordance with those expected.

Treatment of a toluene solution of (171) with an excess of sodium hydroxide effected a carbonyl-forming elimination reaction resulting in the expulsion of acetone and the concomitant formation of (169) in high yield as ascertained by the agreement of all spectroscopic data with those expected.

This series of conversions is depicted in Fig. (42).



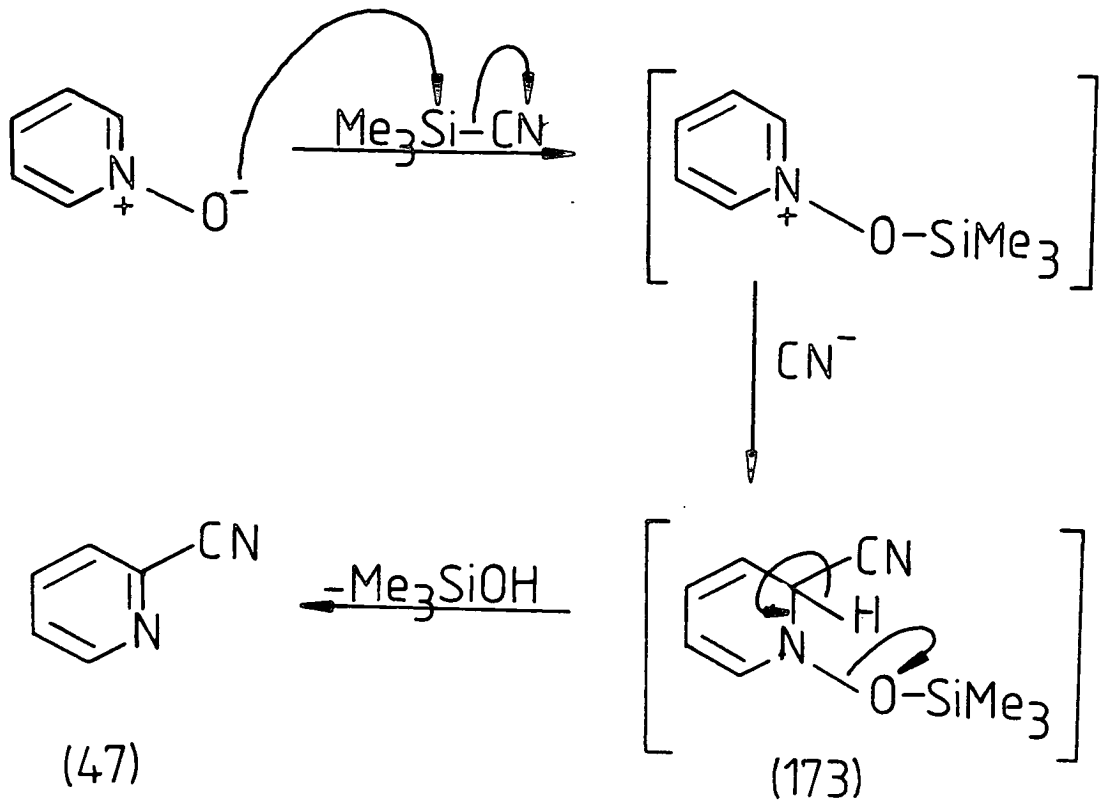
(167) (171) (169)

i 2-Me-but-3-yn-2-ol, $(PPh_3)_2PdCl_2$, CuI, Et_3N
ii NaOH

Fig.(42)

Synthesis of 6,6'-Dicyano-2,2'-Bipyridine (172)

The conversion of (167) to the dicyano-derivative (172) was achieved according to the method commonly used for bromo- to cyano- conversions in the benzene series[93], namely treatment of the bromo compound with an excess of copper(I)cyanide in refluxing DMF. The resulting reaction mixture was poured onto an aqueous solution of sodium



(47)

(173)

Fig. (43)

cyanide and the solid produced removed by filtration and purified by sublimation and recrystallisation in yields of 64-69%.

A variety of 2-cyanopyridines have recently been obtained directly from 2-unsubstituted pyridines by reaction of the derived N-oxides with trimethylsilyl cyanide[94,95,96]. The method is thought to involve transfer of the trimethylsilyl group to the N-oxide function, leading to a siloxypyridinium ion which is activated to nucleophilic attack at the alpha-positions. Such attack by cyanide ion leads to the dihydropyridine derivative (173) which eliminates trimethylsilanol, producing the substitution product (47) as outlined in Fig. (43).

As a method for the preparation of 6,6'-dicyano-2,2'-bipyridine this procedure would have the advantage of starting with the readily available and inexpensive 2,2'-bipyridine, rather than with the 6,6'-dibromo compound which is not easily prepared on a large scale.

2,2'-Bipyridine-di-N-oxide (174) was synthesised from 2,2'-bipyridine (40, R=H) in 91% yield according to the method of Simpson[97] using hydrogen peroxide in acetic acid. Unfortunately, however, treatment of (174) with trimethylsilyl cyanide in DMF afforded only very low yields (5-15%) of the desired 6,6'-dicyano-2,2'-bipyridine (172).

All samples of (172) formed, regardless of the method

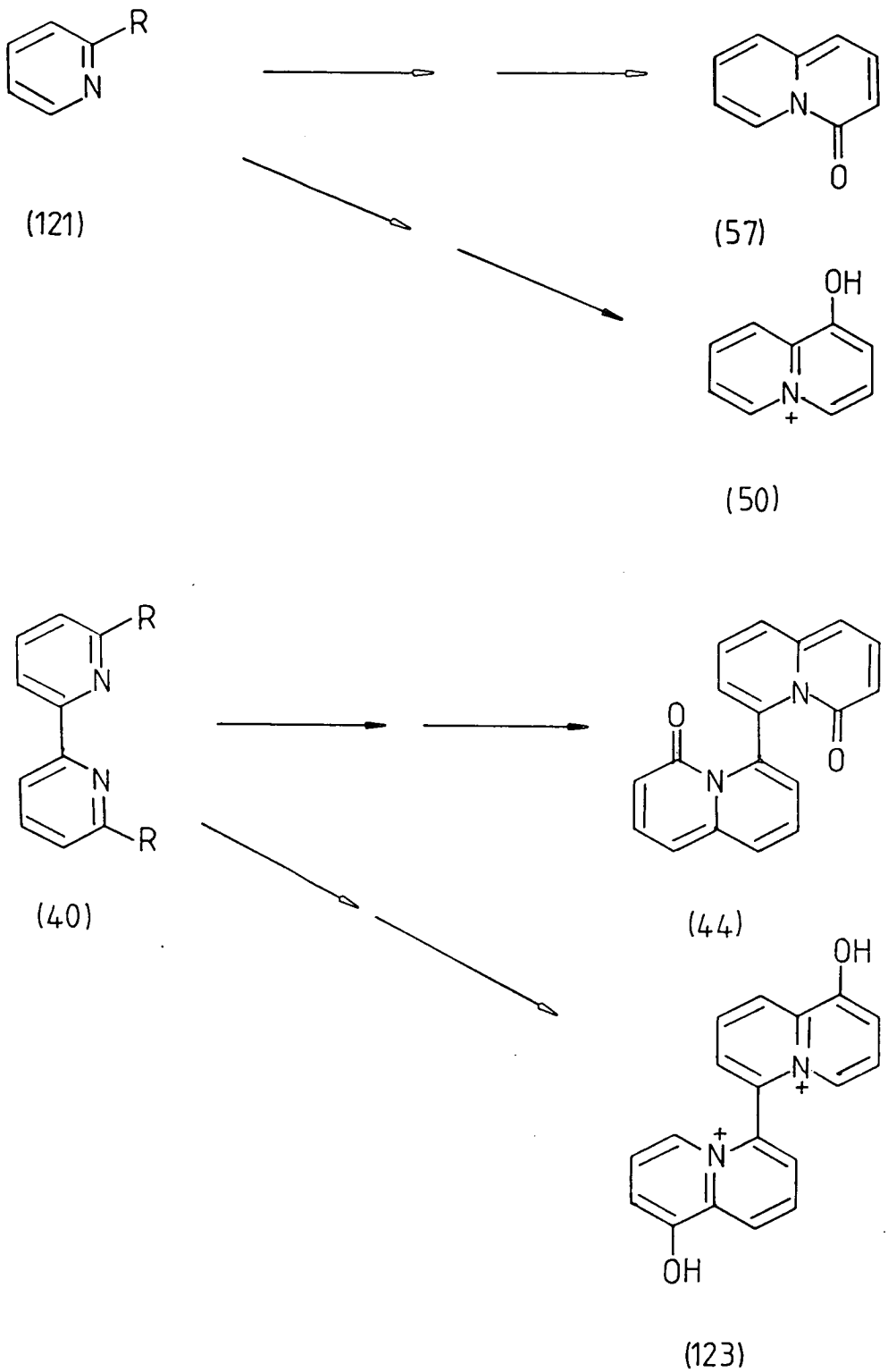
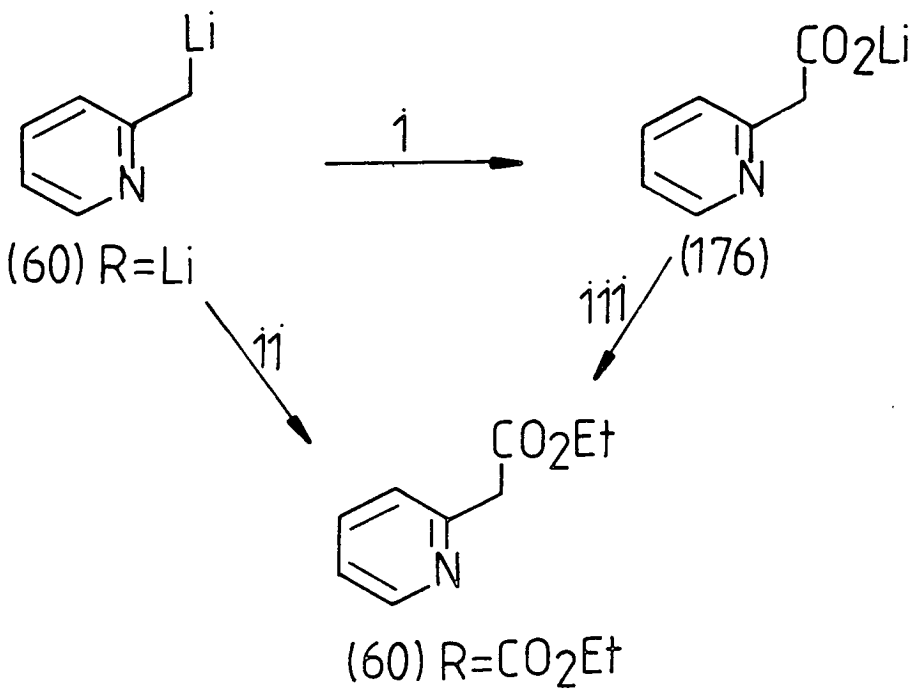


Fig.(44)

of synthesis exhibited spectra in accordance with those expected.

As is apparent from the preceding discussion, the desired bipyridine starting materials for this work are accessible, but only *via* lengthy and experimentally intricate procedures and generally only in moderate yields. The use of model systems, it was hoped, would serve as a means to establish the most suitable chemical reagents and most effective experimental conditions for any proposed reactions before the valuable 6,6'-disubstituted-2,2'-bipyridines were taken further along the proposed synthetic pathways. The obvious model system was the corresponding 2-substituted pyridine. In the model reactions, therefore, the objectives were to modify the 2-substituent of a pyridine by means of efficient chemistry leading to a target of either quinolizin-4-one (57) or 1-hydroxyquinolizinium ion (50). Application of the same conditions to the bipyridines would thereby lead to the key compounds (44) and (123) as indicated in Fig. (44).



i CO_2

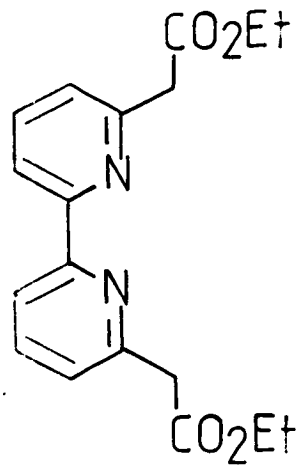
ii $(EtO)_2CO$

iii EtOH / HCl

Fig.(45)

TOWARDS 6,6'-BIS(QUINOLIZIN-4-ONE) (44)

As described in the introduction there are several documented approaches to the quinolizin-4-one system. Indeed one such approach from ethyl 2-pyridylacetate (60, R=CO_2Et), has already been described in Fig. (28). The desired starting material for an analogous approach in the bipyridine series would therefore be (175), which would have to be synthesised from one of the bipyridine starting materials available to us. Thus, although ethyl 2-pyridylacetate is commercially available, an efficient method for its synthesis was sought, with a view to applying the same method to the synthesis of (175).



(175)

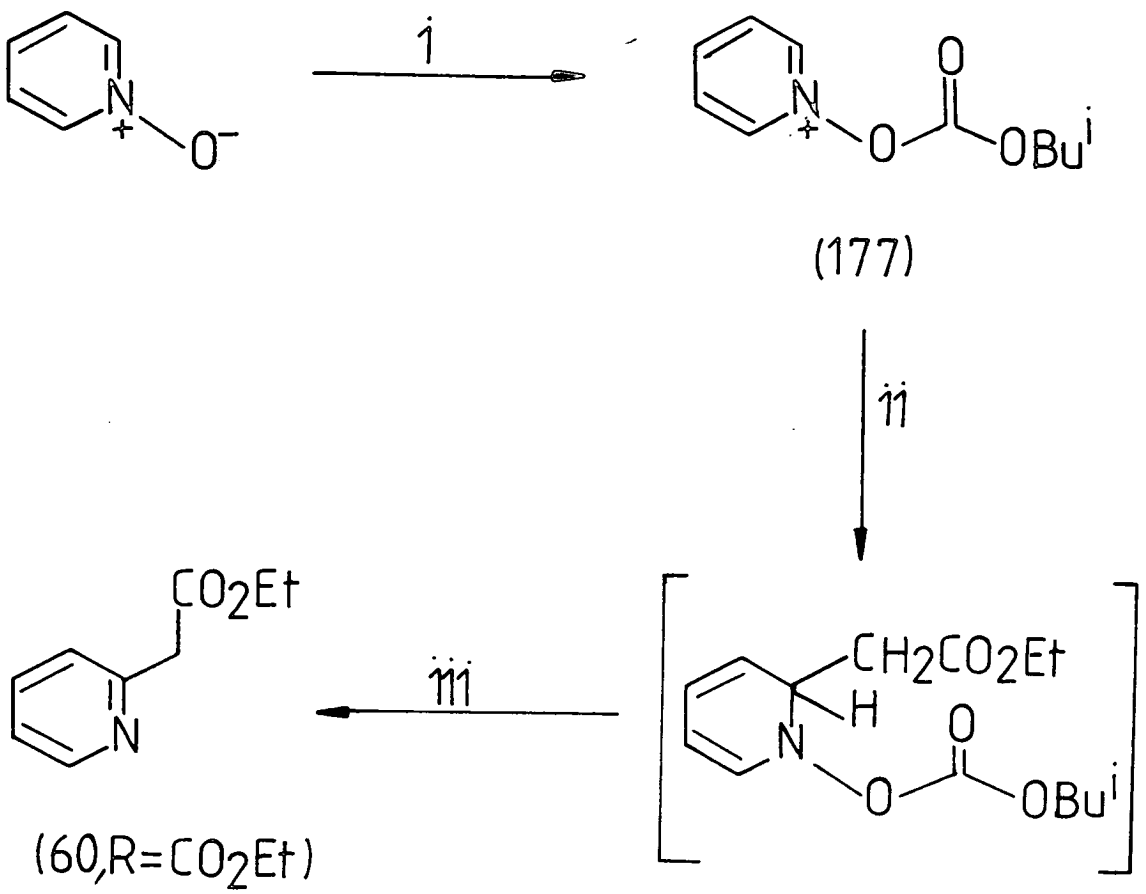
The most commonly used syntheses of ethyl 2-pyridyl-acetate are those of Woodward[98] and Goldberg[99] [Fig. (45)]. The former treated 2-picolyl-lithium (60, R=Li) with solid CO_2 to form the lithium salt of 2-pyridylacetic acid (176). Subsequent esterification with ethanol afforded the desired compound in 35-40% yield. In our

hands, this rather cumbersome procedure resulted in a maximum yield of 21%, perhaps due, in part, to the susceptibility of (176) to decarboxylation.

To avoid the need for an intermediate of the type (176) a method similar to that of Goldberg[99] was tried. To a solution of ethyl chloroformate in ether was added a stoichiometric quantity of ethereal 2-picolyl-lithium. Ethyl 2-pyridylacetate was formed but in a maximum yield of 24% - lower than the 44% achieved by Goldberg on treatment of 2-picolyl-lithium with diethyl carbonate.

Despite the low yields of both these reactions, analogous chemistry was attempted on 6,6'-dimethyl-2,2'-bipyridine (41) because it was envisaged that if (175) could be made, even in low yield, then the bis(quinolizin-4-one) (44) should be attainable in two further steps, which in the case of quinolizin-4-one (57) had gone in high yield [Fig. (28)]. However, the formation of (175) was only detected mass spectrometrically in amounts insufficient for isolation.

In view of the problems associated with the preparation of 6,6'-dimethyl-2,2'-bipyridine (41) and with its conversion to the bis(pyridine acetate) (175) it seemed appropriate to investigate a more speculative approach to (175) based on the readily available 2,2'-bipyridine and proceeding *via* its di-N-oxide. Initially, this approach was based on the work of Vorbrüggen[94,96] and Fife[95] who have used silanes (Me_3SiNu) in order to promote



i $^{i}BuO-C(=O)-Cl$

ii $BrZnCH_2CO_2Et$

iii $-CO_2$, $-{}^{i}BuOH$

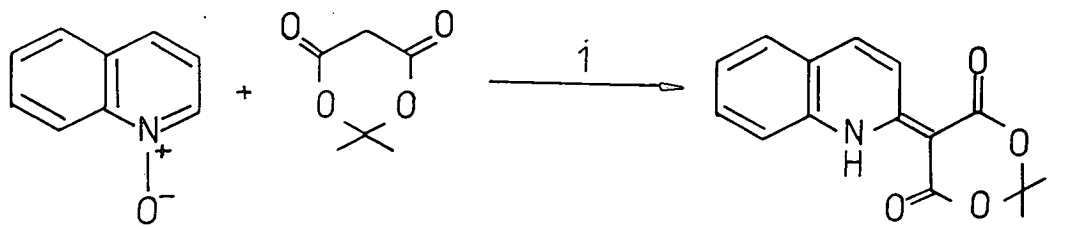
Fig.(46)

attack of carbon-based nucleophiles (Nu) at the 2-position of pyridine-N-oxide. The essential strategy has already been outlined in Fig. (43) and is applicable not only to (Nu = CN) as shown, but also to (Nu = $CH_2CH{=}CH_2$ or CH_2Ph). The silane required for the present purpose, ethyl trimethylsilylacetate is commercially available but its reaction with pyridine-N-oxide had not been reported.

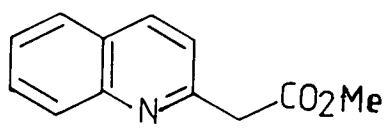
Accordingly, freshly-distilled pyridine-N-oxide was treated with an excess of ethyl trimethylsilylacetate in the presence of fluoride ion according to the method of Vorbrüggen[94,96], but no evidence for the formation of ethyl 2-pyridylacetate was obtained.

A report by Webb[100] concerning the synthesis of 2-substituted pyridines under mild conditions from N-acyloxypyridinium salts (177) and Grignard reagents prompted attempts at the conversion outlined in Fig. (46). The third step was effected by Webb on work-up with aqueous acid. Similar treatment in our case resulted in no product isolation - perhaps due to ester hydrolysis. Subsequent reactions therefore avoided the use of acid, but only resulted in trace amounts of the desired ethyl 2-pyridylacetate.

Hamana and Yousif[101] reported the conversion of quinoline-N-oxide (178) into the corresponding methyl 2-quinolineacetate (181) using Meldrum's acid (179) according to Fig. (47). Although there was no report of the corresponding reaction of pyridine-N-oxide, the same



(178) (179) (180)



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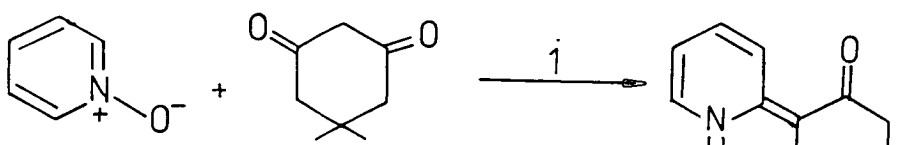


(182) (183)

i Ac_2O

ii MeOH

Fig. (47)

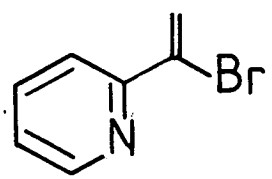
workers reported an analogous reaction of dimedone (182)[102] which, under more severe conditions, reacted with both quinoline- and pyridine-N-oxide to afford condensation products [e.g. (183)] analogous to (180). Thus it was reasonable to assume that reaction of Meldrum's acid (179) and pyridine-N-oxide (124) would occur in a manner parallel to Fig. (47) to produce methyl 2-pyridylacetate.

On addition of Meldrum's acid (in acetic anhydride) to a solution of pyridine-N-oxide in acetic anhydride an initial yellow colour was produced. After addition was complete, the solution had become dark red. Concentration of this gave a dark, intractable gum which was not amenable to chromatography. Distillation of this gum led to extensive charring and to the production of a small amount of a yellow oil which could not be identified. In the light of the work on quinoline-N-oxide (178), the failure of this reaction was disappointing but may have been due, in part, to the lower reactivity of pyridine- compared to quinoline-N-oxide, and to the presence of water in samples of pyridine-N-oxide. Despite the use of freshly-distilled pyridine-N-oxide and the scrupulous exclusion of air, its infra red spectrum indicated the presence of water.

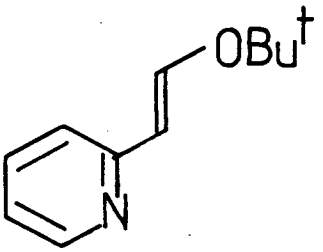
The lack of success of this approach prompted the proposal of alternative routes to the bis(quinolizin-4-one) (44).

Earlier work in these laboratories[103] reported the synthesis of 3-(ethoxycarbonyl)quinolizin-4-one (186) from 2-ethynylpyridine (185) by treatment with diethyl malonate. This approach appeared attractive in view of the recently established synthesis of 6,6'-diethynyl-2,2'-bipyridine (169). First, however, the reported reaction of (185) was repeated with a view to optimising the conditions before attempting it in the bipyridine series.

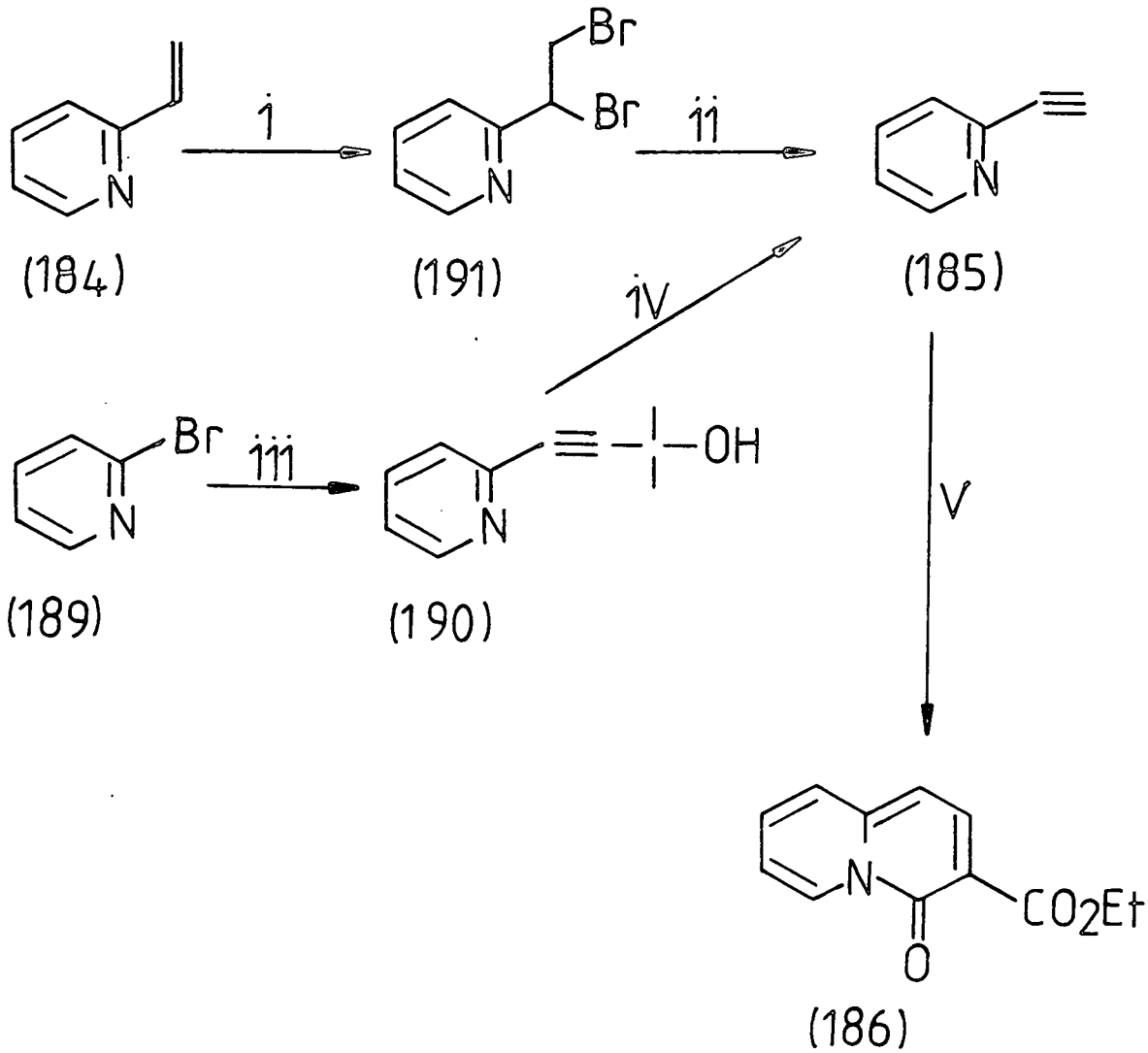
In this work, 2-ethynylpyridine (185) was synthesised by two different methods. The first was that of Leaver and co-workers[103] involving bromine addition to the commercially available 2-vinylpyridine (184) followed by elimination of two moles of HBr with alcoholic potassium hydroxide. However, it was found that the desired product (185) was contaminated, in some cases, with the bromovinyl intermediate (187) and in other cases with the product (188) resulting from the undesirable addition reaction of *t*-butanol to the alkyne (185).



(187)



(188)



(184) (191) (185) (189) (190) (186)

i Br_2

ii KOH, ^tBuOH

iii Base, 2-Me-but-3-yn-2-ol, $(PPh_3)_2PdCl_2$

iv NaOH

v $CH_2(CO_2Et)_2$

Fig.(48)

Separation of (187) from (185) was generally possible by chromatography. However, in cases where (188) was produced, it generally constituted the majority of the product mixture and so separation was not deemed worthwhile.

The second method used in the synthesis of (185) was that of Ames *et al*[92]. and therefore involved the treatment of 2-bromopyridine (189) with 2-methyl-but-3-yn-2-ol (170) in diethylamine in the presence of bis(triphenyl-phosphine)palladium(II) dichloride and copper(I) iodide to form (190) in 74% yield. This was then treated with base in refluxing toluene, affording (185) in 65% yield.

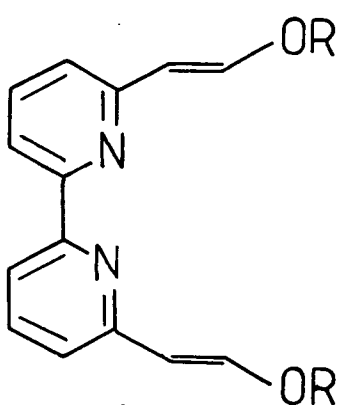
Both of these approaches to (185) are detailed in Fig. (48) and all three isolated products were identified by means of proton n.m.r., infra red and mass spectra.

The reaction of (185) with diethyl malonate was carried out under a variety of conditions. It was found that potassium-*t*-butoxide was a better base than sodium ethoxide or sodium hydride. Yields were further improved when diethyl malonate was used in two-fold excess. It was also found that prolonged heating resulted in poorer yields. Thus the optimised reaction conditions for the conversion of (185) to (186) were established. To a warm solution of potassium-*t*-butoxide was added diethyl malonate, followed by 0.5 molar equivalent of 2-ethynyl-pyridine. The resulting solution was heated at reflux for

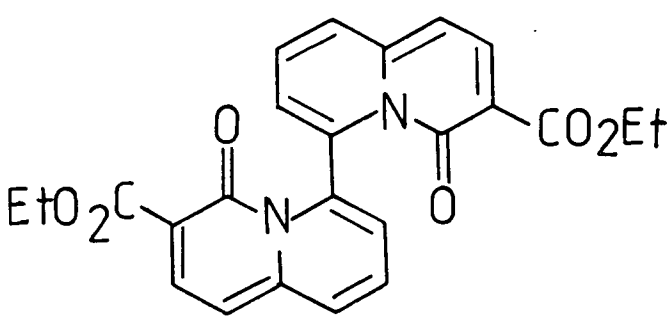
10h, extracted into dichloromethane from water, purified by chromatography on silica and recrystallisation from ethanol giving 55% of pure (186).

These conditions were then applied to the reaction of 6,6′-diethynyl-2,2′-bipyridine (169) with diethyl malonate. The length of reflux was extended because analysis of the reaction mixture by t.l.c. at 10h indicated the presence of starting material. After 20h at reflux, this had all been consumed and work up of the reaction afforded 30% of 6,6′-di-(*t*-butoxyvinyl)-2,2′-bipyridine (192, R=*t*-Bu) as identified by mass spectrometry [m/z 352(M^+), 279 (M-*t*-BuO)]. Accurate mass measurement and the 200 MHz proton n.m.r. spectrum were also in accordance with this structure.

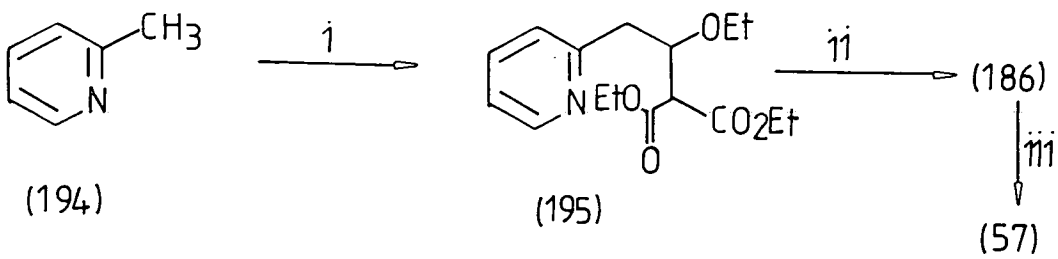
Investigation of the FAB mass spectrum of the only other isolated material in this reaction revealed an (M+1) peak at m/z 433, consistent with 6,6′-bis (3-ethoxycarbonyl-quinolizin-4-one) (193). The presence of additional peaks, however, implied significant impurity and (193) could not be isolated.



(192)

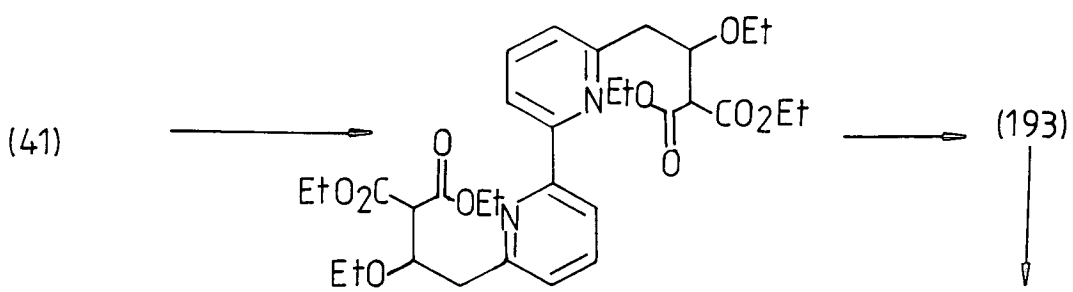


(193)



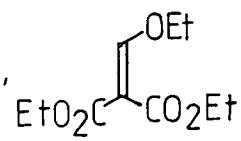
(194)

(195)



(196)

i n-BuLi,



ii Δ

iii 5M HCl

Fig.(49)

For the sake of comparison, this reaction was repeated using sodium ethoxide as the base. This resulted in the isolation of 60% of the 6,6'-di(ethoxyvinyl)-2,2'-bipyridine (192, R=Et) as identified by FAB mass spectrometry: m/z 297 (M+1), 251 (M-OEt). The proton n.m.r. exhibited two doublets and a triplet in the aromatic region as well as vinylic doublets at δ6.45 and 5.65 and ethyl signals. Likewise, the use of sodium methoxide produced small amounts of (192, R=Me) as identified by FAB mass spectrometry: m/z 269 (M+1), 237 (M-OMe) and proton n.m.r. showing vinylic doublets and a methyl singlet at δ3.90. In all cases, small amounts (5-15%) of unreacted starting material was recovered.

The failure of these reactions was disappointing in view of the effort expended on the model system which, it would appear in this case, is not truly representative of the reactivity of the bipyridine analogues.

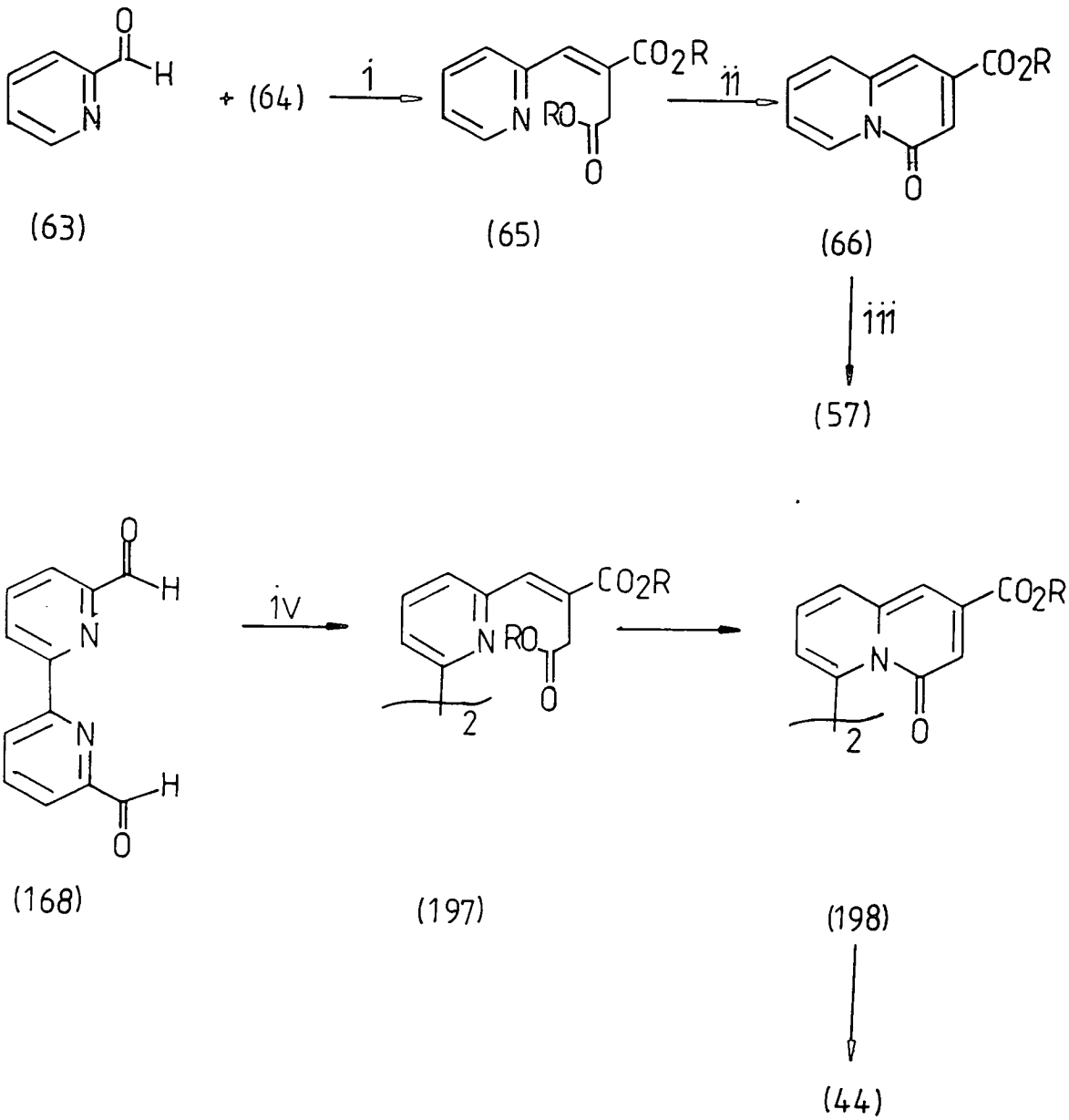
In parallel with the preceding approach to the bis-(quinolizin-4-one) (44), the method outlined in Fig. (49) was also attempted.

The reaction of 2-picoline (194) to form (186) was described in minimal detail in a patent by Kitaura *et al*[104]. The chemistry was repeated with a view to optimising conditions prior to trial on the bipyridine starting material (41). An overall 45% yield of (186) could be obtained by treatment of (194) with *n*-butyl-

lithium and a molar equivalent of diethyl ethoxymethylene-malonate (128) at ice bath temperature. Addition of acetic acid followed by concentration under vacuum led to the crude (195). Attempts to purify this led to mixtures of (186) and (195) and it was found to be more convenient to carry out the subsequent thermal cyclisation (in diphenyl ether/biphenyl) on the crude material. The identity of (186) was established by the usual spectroscopic methods and by direct comparison with (186) formed by the previously discussed method.

Treatment of (41) with two molar equivalents of *n*-butyl-lithium followed by (128) led to the formation of the desired (196) in 60% yield, as established by n.m.r. This was not purified, and when subjected to thermolysis in biphenyl and diphenyl ether, no cyclisation of the crude sample was effected, as determined by t.l.c. Purification of the crude (196) was accomplished by dry flash column chromatography on silica. However, cyclisation of the purified sample could not be effected by the thermolysis procedure previously applied, nor by flash vacuum pyrolysis at 600°C/5 x 10^{-3} mm nor 800°C/2 x 10^{-2} mm.

One further approach to the desired bis(quinolizin-4-one) (44) utilised the recent work of Linke *et al*[34] who synthesised 2-(ethoxycarbonyl)quinolizin-4-one (66) from 2-formylpyridine (63) by treatment with the phosphonate (64) in a Horner-Wittig reaction as outlined in Fig. (11)



i Base
ii TsOH
iii HCl
iv 2x(64), Base

Fig.(50)

[repeated in Fig. (50) for convenience]. As described earlier, the 6,6'-diformyl-2,2'-bipyridine starting material required (168) had been synthesised in this work, and so Fig. (50) represented a realistic proposal with good literature precedent.

The phosphonate (64) was synthesised in 87% yield according to the method of Linke[34], involving the treatment of diethyl phosphite with sodium, followed by the dropwise addition of a molar equivalent of freshly distilled diethyl maleate. Its identity was verified by means of mass spectrometry and proton n.m.r. which showed typical ethyl signals and in addition some two- and three-bond P-H couplings.

In a typical model reaction, molar equivalents of 2-formylpyridine (63) and the phosphonate (64) were added to a solution of sodium ethoxide at 0°C. After 1h stirring at ambient temperature, aqueous extraction followed by column chromatography on silica yielded 62% of the desired product (65) which was identified by means of mass spectrometric and proton n.m.r. data and comparison of these with the spectroscopic data given in the literature[34]. The cyclisation was achieved in 91% yield using *p*-toluenesulphonic acid in refluxing toluene.

This method was extended to the bipyridine series resulting in a 50% yield of the Horner-Wittig product (197) as unambiguously determined by infra red and mass spectrometry as well as proton n.m.r. and elemental

analysis.

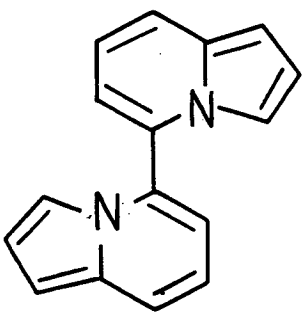
Repetition of the procedure using the phosphonate (64, R-Me) gave the methyl analogue of (197) - again fully characterised by all the normal spectroscopic and analytical methods.

The cyclisation of (197) proved problematic as the following description details. Toluene reflux in the presence of *p*-toluenesulphonic acid caused no change in the t.l.c. of the solution. The failure of this reaction led to the proposal that a catalyst more selective for co-ordination with the ester oxygen than with the ring nitrogen might be more effective. Accordingly Lewis acids such as titanium tetrachloride [either alone or with titanium tetrakis(isopropoxide)] and boron trifluoride diethyl etherate were used in subsequent attempts, but no reaction was observed in any of these cases.

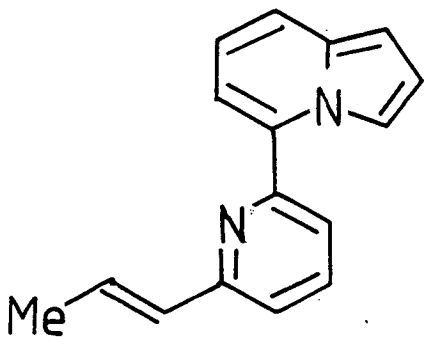
The use of thermal methods was subsequently attempted. After five hours at reflux in diphenyl ether/biphenyl, t.l.c. indicated the presence of some material other than (197). The reaction mixture was subjected to dry flash chromatography resulting in the isolation of a small amount of material exhibiting mass spectrometric peaks consistent with the cyclisation of one of the rings (m/z 478) and both of the rings (m/z 432). However, the presence of the starting material was also in evidence from a small parent ion peak at m/z 524 and a number of fragment ion peaks (m/z 479, 434). The isolation of the

constituent compounds of this mixture could not be achieved on account of their low yield.

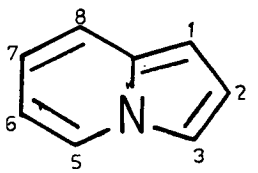
The subjection of (197, R-Et) to flash vacuum pyrolysis at a furnace temperature of 820°C and a vacuum of 10^{-3} mm resulted in the production of a highly fluorescent material which, after chromatography under argon, afforded a light- and air-sensitive substance with a mass spectrum exhibiting peaks at m/z 232 and 234. These were tentatively assigned to the presence of bis-(indolizine) (199) and 5-[6-(propenyl)-2-pyridyl]-indolizine (200). Accurate mass measurement on m/z 232 indicated an empirical formula of $C_{16}H_{12}N_2$ - consistent with that of (199).



(199)



(200)



(201)

Proton n.m.r. at 200 MHz indicated the absence of ethyl protons and the possible presence of two compounds. A proton signal at δ8.20-8.10 contained eight equally-spaced lines suggesting three coupling constants of relative magnitudes 1:2:4. In fact the three calculated J-values were 0.72 Hz, 1.44 Hz and 2.82 Hz.

Interestingly, indolizine itself (201) is light- and air-sensitive and its H-atom at position-3 exhibits a comparable set of coupling constants; $J_{3,8}$ = 0.5 Hz; $J_{3,1}$ = 1.2 Hz; $J_{3,2}$ = 2.74 Hz (ref. 105).

A second, less intense set of eight similarly-spaced lines was evident at δ8.08-8.01. This, along with the presence of two doublets of doublets at δ2.19-1.89 supported the possible existence of (200). The possibility of *cis* or *trans*-isomers of (200) means that the methyl signal would appear as a doublet of doublets in each case, and the signals at δ2.19-1.89 were tentatively assigned to this methyl group, the coupling constants being assigned as follows;

Cis-isomer : $^{3}J_{gem}$ = 6.2 Hz; $^{4}J_{trans}$ = 1.0 Hz

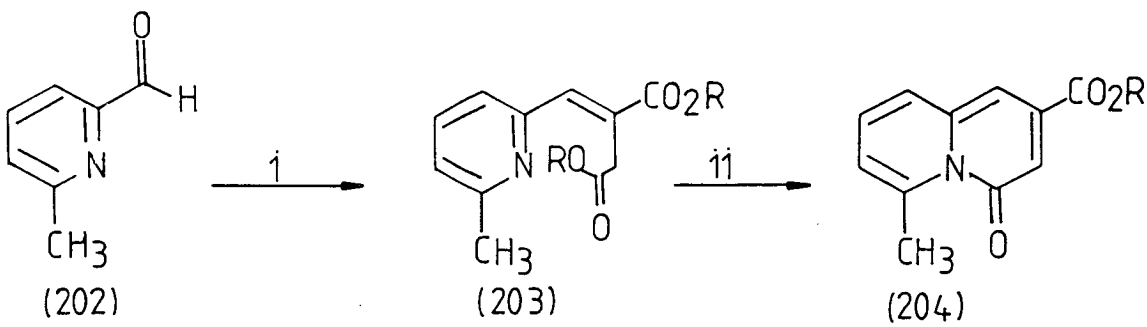
Trans-isomer : $^{3}J_{gem}$ = 7.1 Hz; $^{4}J_{cis}$ = 1.64 Hz

In both isomers, the vinyl protons should each appear as a doublet of quartets. Evidence for one such signal was seen at δ6.25-5.90. However, no other signals of this type were discernable from the rest of the spectrum.

Isolation of compounds (199) or (200) could not be achieved owing to their sensitivity to light and air.

Flash vacuum pyrolysis of the methyl ester of (197) was also attempted. It was hoped that the inability of such a compound to lose ethene by thermal elimination from the ester groups would lead to the formation of the methyl ester of (198). However, none of the desired product was detected.

It would seem, from the foregoing discussion, that cyclisation of a suitable precursor to form the key compound (44) or its ester derivative (198) is a highly unfavourable process. The reasons for this may be steric or electronic. It is worthy of note at this point that Linke[34] quoted very low yields (*ca* 5%) for the conversion illustrated in Fig. (51). Almost certainly the principal factor inhibiting cyclisation in this case is steric hindrance from the 6-methyl group. It is not unreasonable, therefore to assume that similar factors are involved in the case under consideration in this work.



i (64), NaH, 58% yield

ii p-TsOH, < 5% yield

Fig.(51)

TOWARDS 6,6'-BIS(1-HYDROXYQUINOLIZINIUM)ION (123)

The synthesis of quinolizinium salts and their 1-hydroxy derivatives has been extensively studied (see introduction). In this work, it was envisaged that (123) would be synthesised from suitable bipyridine starting materials by means of chemistry previously established in the model system. The objective in the model system would therefore be the synthesis of a quinolizinium nucleus free from all substituents other than a 1-hydroxy function, and utilising chemistry which would avoid the problematic dehydrogenation step common to a number of quinolizinium ion syntheses. 1-Hydroxyquinolizinium bromide (50) can be obtained in 5 steps from 2-cyanopyridine[25,106] but it was hoped that the procedure outlined in Fig. (52) would provide a much shorter and more efficient route to this compound. Instead of the reaction with 3-ethoxypropyl-magnesium bromide, as in ref. (106), 2-cyanopyridine (47) was treated with the Grignard reagent (205) to form ketone (206). Purification of this compound was problematic, as ascertained by extraneous peaks in both ^{13}C and ^{1}H n.m.r. spectra, leading to yields of the order of 45%. The ketone was characterised by the usual spectroscopic means. Attempts to convert it into the desired salt (50) were made using HBr, or solutions of HCl in acetone or acetic acid, but no reaction was observed. Treatment of an acetic acid solution of (206) with perchloric acid yielded 60% of (207) exhibiting spectra in accordance with the

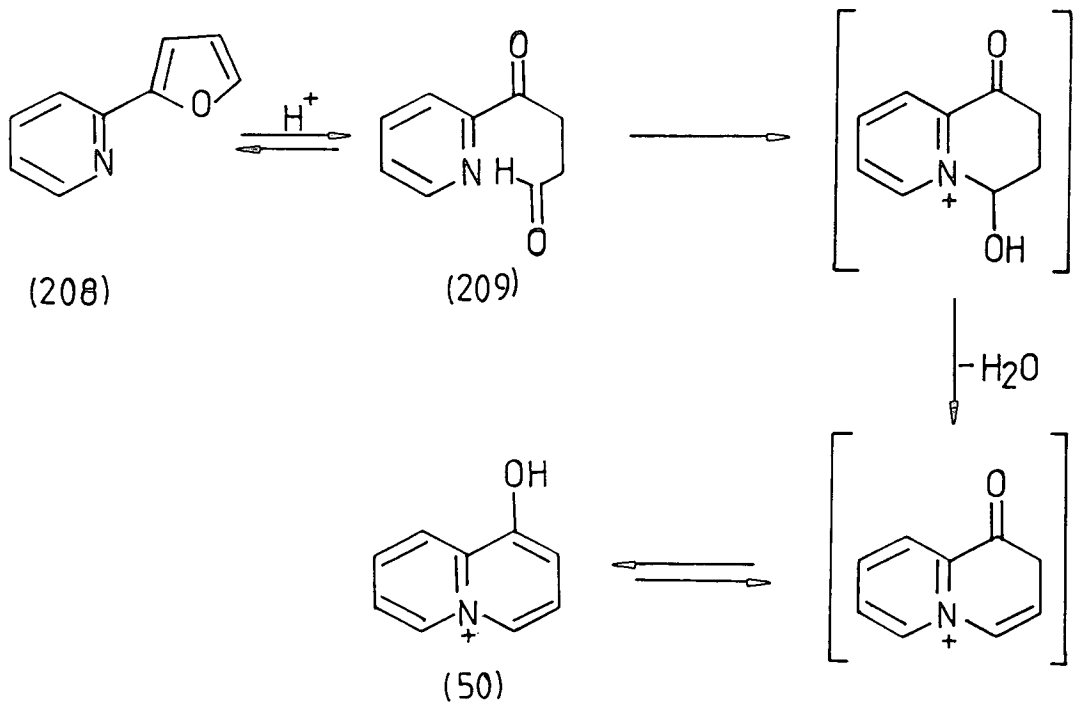
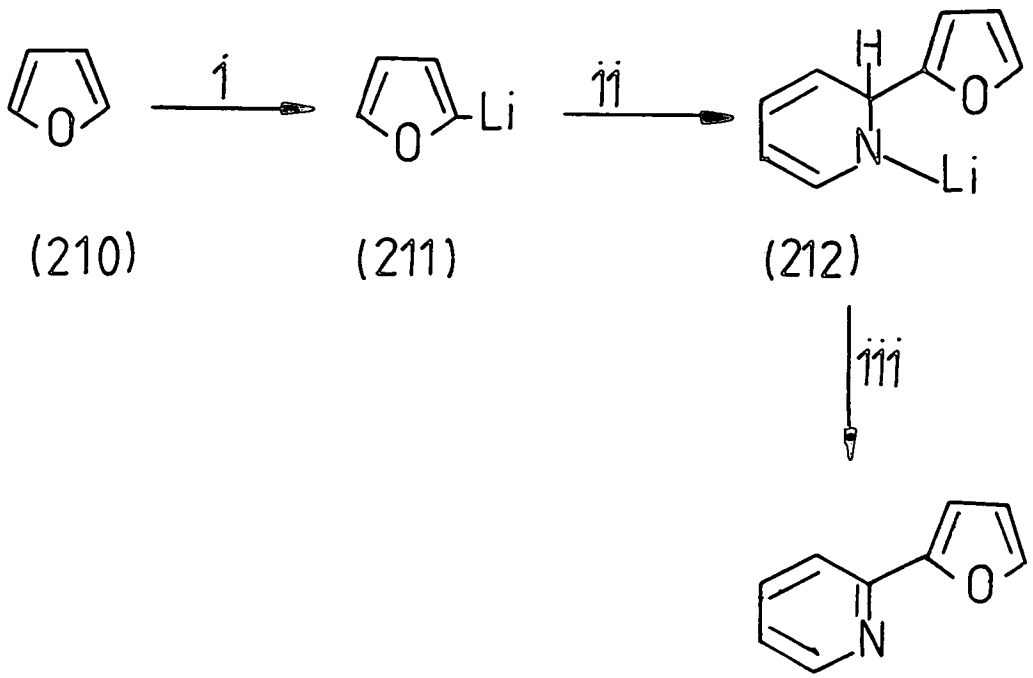


Fig.(53)

structure shown in Fig. (52). The spectra of (207) indicated a level of purity which had been unattainable for (206) and so all samples of (206) were converted to the corresponding pyridinium perchlorate to ensure high purity. Attempts to convert (207) to (50) involved heating in a solvent in the presence of acid, the intention being to release the protected aldehyde function which was expected to undergo cyclo-dehydration at the pyridine nitrogen. After 20h at 80°C, t.l.c. indicated the formation of some product but attempts to isolate this material led only to the production of a small amount of brown solid which decomposed on removal of solvent. The identity of this solid could not be established but its sensitivity as described is not consistent with (50) which is a stable, white crystalline solid.

The ketoaldehyde (209) envisaged as the immediate precursor of (50) in Fig. (52) could also be derived, in principle, by an acid-catalysed ring-opening of the furyl group in 2-(2-furyl)pyridine (208). Although such ring-opening reactions are reversible, it seemed possible that even a small equilibrium concentration of (209) would undergo irreversible cyclodehydration to yield the 1-hydroxyquinolizinium ion (50) according to Fig. (53).

Initial attempts to synthesise (208) made use of the work of Ramanathan[107] and that of Dietrich-Buchecker[108]. Treatment of a chilled solution of furan (210) with *n*-butyl-lithium generated 2-furyl-lithium (211) which was



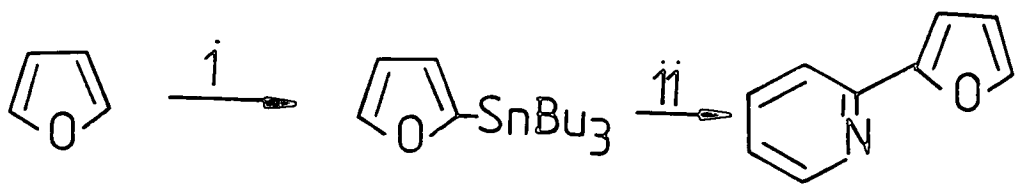
(210) (211) (212) (208)

i n-BuLi

ii pyridine

iii [O]

Fig.(54)



(213) (208)

i n-BuLi, Bu_3SnCl

ii 2-Br-pyridine, $(PPh_3)_2PdCl_2$

Fig.(55)

treated with a molar equivalent of pyridine. This was expected to yield a solution of the adduct (212) according to Fig. (54). The subsequent oxidative step was attempted in this work using MnO_2[108], hydrogen peroxide, phenanthraquinone[109] or air. However, none of the desired (208) was isolated.

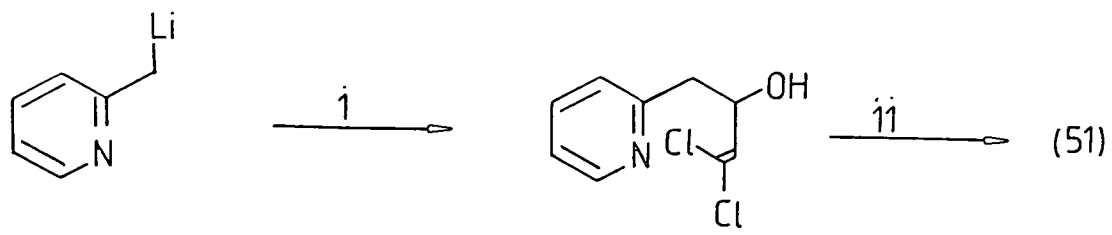
The failure of this approach prompted the search for other modes of coupling heterocyclic rings. Many such couplings are reported and generally involve the transition-metal-catalysed reaction between one suitably halogenated and one suitably metallated heterocycle. The method of choice was that of Bailey[110] and involved the treatment of 2-(tributylstannyl)furan (213) with 2-bromopyridine (189) in the presence of bis(triphenylphosphine)palladium(II) dichloride as indicated in Fig. (55). The effective catalyst is believed to be a Pd(0) species which is formed by reduction of Pd(II) *in situ*.

Compound (213) was prepared in 69% yield according to the method Pinhey and Roche[111], involving the treatment of a cooled solution (-30°C) of furan in tetrahydrofuran with *n*-butyl-lithium, followed by the addition of one molar equivalent of tri-*n*-butyl(chloro)stannane. This preparation could be done on a large scale, and all spectroscopic data agreed with those reported.

The synthesis of (208) was achieved by treating a solution of 2-bromopyridine in tetrahydrofuran with a molar equivalent of (213) in the presence of a catalytic

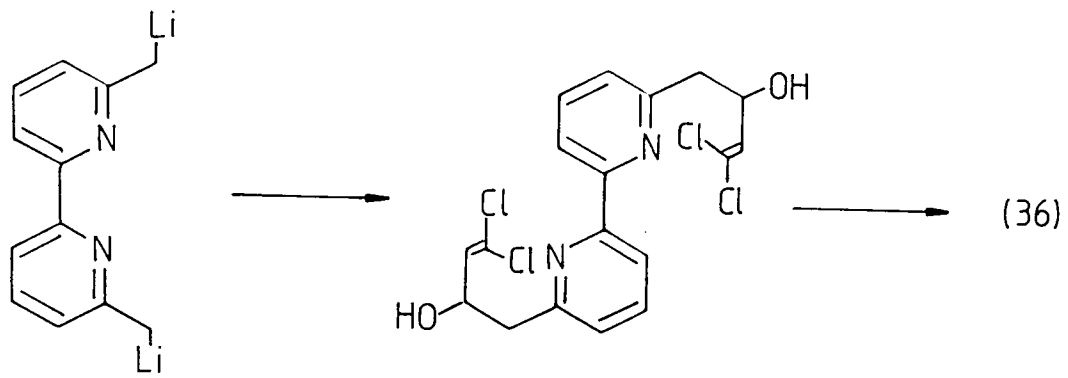
amount of bis(triphenylphosphine)palladium(II)dichloride. After a 20h reflux followed by dry flash chromatography, typically 50% of pure (208) could be isolated, along with considerable amounts of starting materials which, when refluxed with fresh catalyst for a further 20h period, yielded another 20% of pure product. Interestingly, the use of tetrakis(triphenylphosphine)palladium(O) in conjunction with a trace of zinc iodide resulted in lower yields than the overall 70% obtained with the Pd(II) catalyst. The identity of (208) was verified by proton n.m.r. infra red and mass spectrometry.

Treatment of an acetic acid solution of (208) with perchloric acid did not lead to the desired 1-hydroxy-quinolizinium salt (50), but simply to the protonated form of (208) in high yield, as ascertained by proton and carbon-13 n.m.r. and mass spectrometry. The infra red spectrum showed no evidence of OH stretching. Unfortunately, lack of time prohibited the investigation of alternative methods of ring cleavage. However, in the light of the difficulties generally experienced in effecting cyclisation in the bipyridine series, as described earlier in this work, the failure of the cyclisation on the model system offered little hope of its success in the bipyridine series.



(60, R=Li)

(215)



(216)

(217)

i (214) = ß,ß- dichloroacrolein.

ii Δ

Fig.(56)

TOWARDS 6,6'-BIS(4-HALOGENOQUINOLIZINIUM)ION (36)

As is evident from Figs. (4) and (7), compound (36) was envisaged as a key intermediate in the synthesis of the [18]-annulene target (20). However, in both of these schemes it was proposed that it would be obtained from either 6,6'-bis(quinolizin-4-one) (44) or the thiocarbonyl analogue (35). As described earlier, numerous difficulties have prevented the synthesis of (44), thus a method whereby compound (36) could be synthesised directly from a bipyridine precursor offered obvious attractions.

To this end the following model reaction, based on a related report by Ila and co-workers[112], was proposed, with a view to extending it to the bipyridine series as depicted in Fig. (56).

Treatment of 2-picolyl-lithium (60c, R=H) with (214)[113] at -78°C under an inert atmosphere resulted in the formation of a dark brown solution. Treatment with ammonium chloride solution followed by column chromatography on alumina afforded the carbinol (215) in 62% yield as verified by proton n.m.r. infra red and mass spectrometry as well as elemental analysis.

Dehydration and cyclisation of (215) was attempted by refluxing either alone or in the presence of *p*-toluene-sulphonic acid, formic acid or boron trifluoride diethyl etherate, but such treatments had no effect at all, allowing starting material (or its protonated form) to be recovered in each case. However, the Lewis acids $AlCl_3$

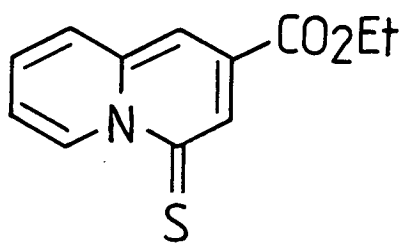
and $FeCl_3$ were found to effect the cyclisation in 20% and 43% respectively, as verified by comparison of spectroscopic data with those of (51) obtained previously in this work.

Once again, in the light of the aforementioned difficulties in effecting the desired cyclisation reactions in the bipyridine series, this line of work was not extended to the latter series in the belief that steric factors would preclude its success.

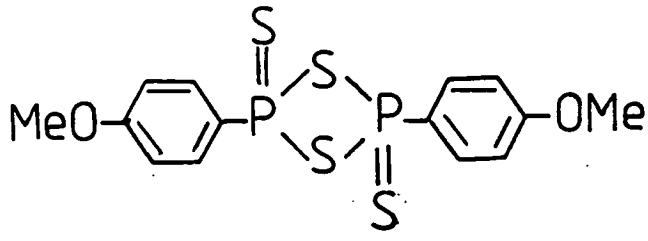
THE SYNTHESIS AND OXIDATION OF SOME QUINOLIZINE-4-THIONES

As outlined in Fig. (38), if the 6,6'-bis(quinolizine-4-thione) (35) had been synthesised, it was envisaged that direct coupling at the thiocarbonyl carbon atoms would have effected the synthesis of (20). As for many of the previously described reactions, such a coupling was attempted on a model system in the first instance. To this end, the copper-mediated coupling of 2-(ethoxycarbonyl)quinolizine-4-thione (218) was attempted. In the event, there was no requirement for such a reaction since (35) could not be synthesised. However, some interesting results did emerge and as such are included here for discussion.

The synthesis of (218) was effected in quantitative yield by treatment of 2-(ethoxycarbonyl)quinolizin-4-one (66) with Lawesson's Reagent (219) in refluxing toluene.



(218)



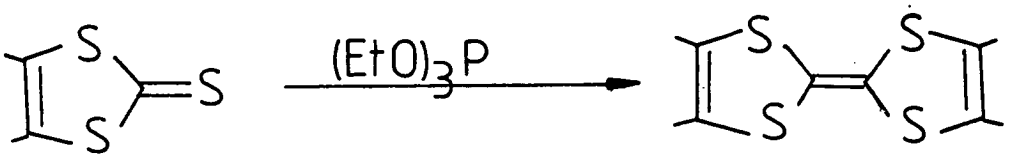
(219)

All recorded spectra were in accordance with the structure illustrated. One spectroscopic feature characteristic of (218) and other quinolizine-4-thiones is the presence of a finely split doublet due to H-6 at ~ δ10.5 in the proton n.m.r. spectrum.

It has been known for some time[114] that certain thioketones, when subjected to heat in the presence of copper, yield the corresponding olefinic derivatives and cupric sulphide

e.g. $2Ar_2C{=}S+2Cu \longrightarrow Ar_2C{=}CAr_2+2CuS$

Schönberg and co-workers[115] modified the process and obtained a purer product by refluxing the thioketone with copper bronze in toluene or xylene solution. More recently, Narita and Pittmann[116] reported the synthesis of tetrathiafulvalenes (23) by refluxing the dithiolethione precursors (220) in triethyl phosphite.



(220) (23)

In this work, it was found that heating under reflux with triethyl phosphite effected no reaction, as determined by t.l.c. Refluxing in xylene in the presence of copper bronze, however, resulted in the formation of a compound showing a slow-moving, highly fluorescent spot on t.l.c. The proton n.m.r. spectrum of this isolated material was very complex and indicated the probable presence of two different compounds. However, mass spectrometry showed one major peak at m/z 217, consistent with the presence of 2-(ethoxycarbonyl)quinolizin-4-one (66) as a result of oxidation of starting material.

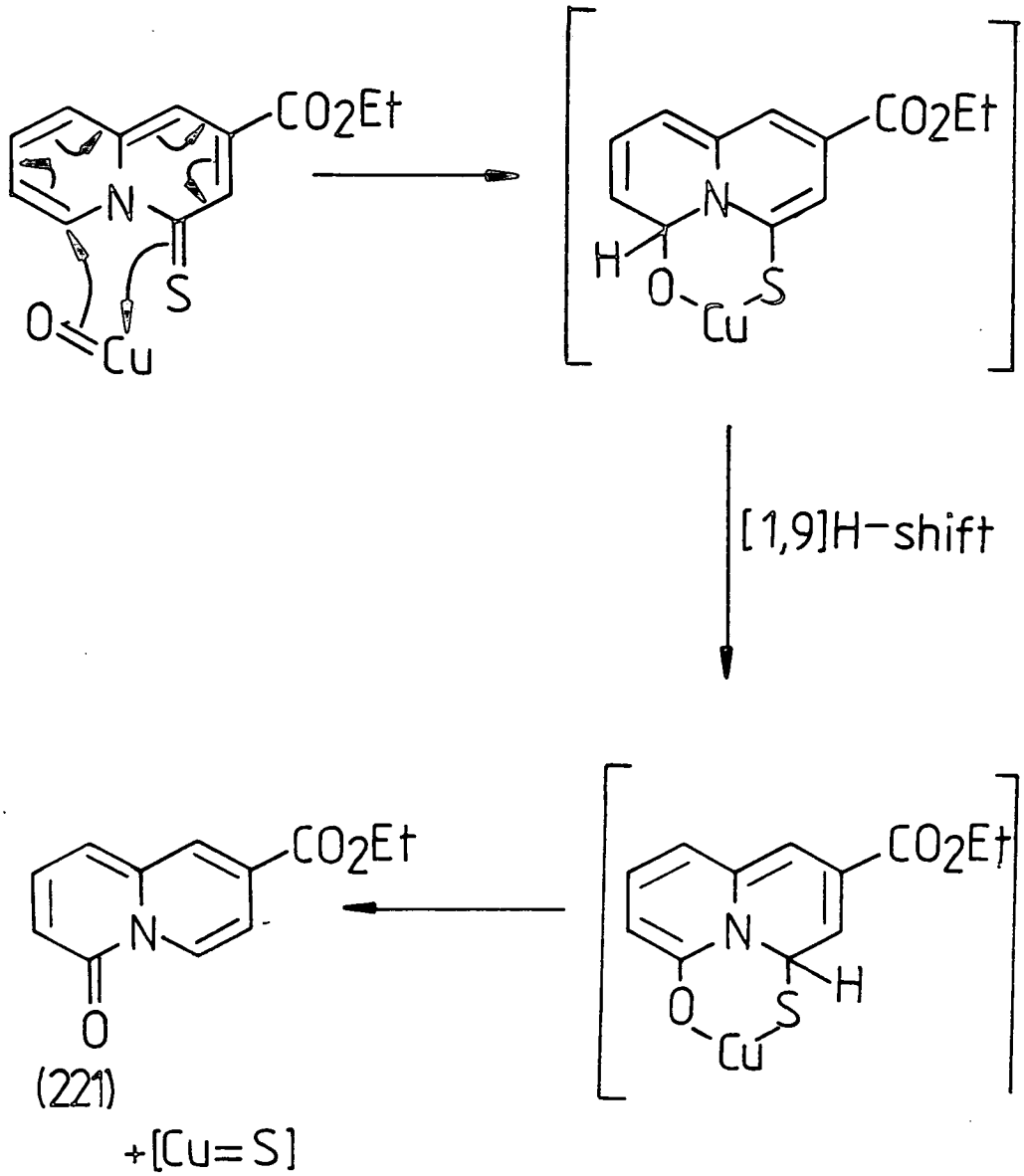


Fig.(57)

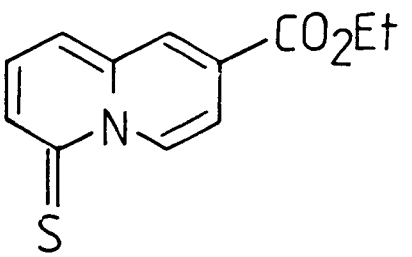
Detailed analysis of the proton n.m.r. spectrum, and comparison with that of an authentic sample of (66) verified the presence of this compound and revealed six additional aromatic proton signals which were consistent with the presence of an isomeric quinolizone (221). Lack of resolution prevented the complete assignment of the spectrum and hence total verification of the existence of (221).

It was proposed that such an isomerisation might have been brought about by the involvement of copper(I)oxide, known to exist in a layer 6-7 A° deep on the surface of copper[117]. If the species present at the surface of the copper could be formally regarded as [Cu=O], then the conversion outlined in Fig. (57) represents a possible mechanism whereby (221) could be formed. Alternatively, it was recognised that the isomerisation might have been unrelated to the presence of copper and that a similar mechanism involving singlet oxygen [O=O] ought to be considered.

In an effort to ascertain the cause of the isomerisation, a solution of (218) in the presence of air was subjected to tungsten filament lamp irradiation, 366 nm irradiation and sunlight. However, none of these caused the formation of (221) or (66) as verified by t.l.c. Compound (218) was refluxed in xylene in the presence of copper(I)oxide for 100h and the concentrated reaction mixture subjected to preparative t.l.c. This

◊ ○ (218) & (222)
of
Hnmr (360MHz)
PPM
10.4
8.4
8.2
8.0
PPM
7.8
7.6
7.4
7.2

resulted in an orange band of the same Rf as starting material (218) and a yellow band of the same Rf as that of the (66)/(221) mixture obtained previously. Examination of the orange material by proton n.m.r. at 360 MHz led to the identification of (218), by comparison with an authentic spectrum, and one other quinolizine-4-thione as diagnosed by the presence of an additional, finely split doublet at δ10.4. Subtraction of the signals due to (218) led to a spectrum fully consistent with the existence of isomerised starting material (222). It was proposed that such isomerisation had occurred as a result of the attack of [Cu=S], formed according to Fig. (57), on a molecule of (218) in the same manner as the proposed attack of [Cu=O].



(222)

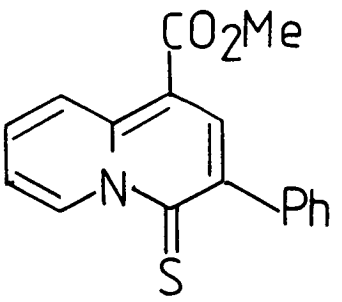
Examination of the 360 MHz proton n.m.r. spectrum of the yellow product verified the presence of (66) and its isomer (221). Subtraction of the signals known to be due to (66) led to a spectrum which could be fully assigned to structure (221), as shown.

The use of integrals allowed the yields of (218), (222), (66) and (221) to be assigned respectively 23%, 12%, 5% and 7%.

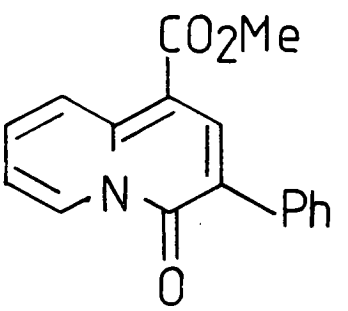
^{1}H nmr (360MHz)
of
(66) & (221)
◇
○

Reactions of (218) with other metal oxides, namely those of Ag(I), Cu(II), Ni(II) and Zn(II), in refluxing xylene were carried out. All resulted in conversion to (66) in varying yields, but only in the case of Cu(II)oxide was any of the isomer (221) detected. In none of the cases was isomerised starting material (222) produced.

With a view to extending the investigation, the reaction of (223)[118] in refluxing xylene was monitored. As expected, oxidation to (224) occurred but no isomerisation of (223) or the oxidised form (224) was detected in the presence of Cu(I) or Ag(I)oxides.

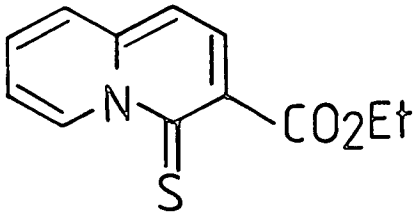


(223)

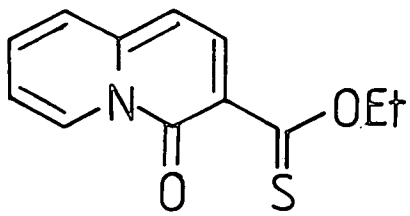


(224)

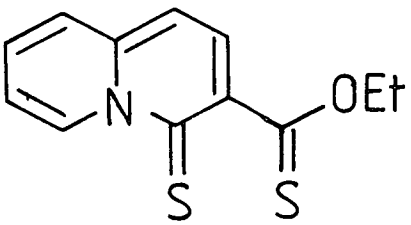
The 3-(ethoxycarbonyl)quinolizine-4-thione (225) was unknown, but a compound worthy of inclusion in this study. In an effort to synthesise it, 3-(ethoxycarbonyl)-quinolizin-4-one (186) was treated with a molar equivalent of Lawesson's Reagent (219) in refluxing toluene. Three products were isolated namely (226), (227) and a trace of material isomeric with (227), tentatively formulated as



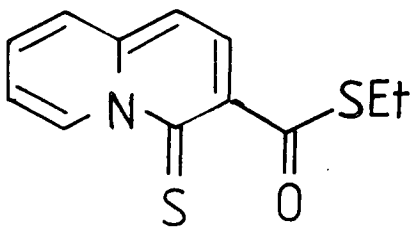
(225)



(226)



(227)



(228)

(228).

Compound (226) showed a molecular ion at m/z 233 and a proton n.m.r. spectrum very similar to that of (186) and lacking the doublet at ~ δ10.5, diagnostic of a 4-thione group. Compound (227) gave a proton n.m.r. spectrum exhibiting the characteristic finely split doublet at high δ. This established the presence of a 4-thione group, and elemental analysis, together with a molecular ion peak at m/z 249 in the mass spectrum showed that two of the oxygen atoms of (186) had been replaced by sulphur. The chemical shift of the CH_2 protons was δ4.78, showing the presence of OEt and establishing the structure as (227).

Comparison of the carbon-13 n.m.r. spectra of (226) and (186) showed one major difference. The signal due to the ester carbonyl in (186) occurred at δ165.5 whereas in the thionester analogue (226) this signal occurred at δ209.8. These values are in agreement with the empirical equation derived by Lawesson[119] which states that, for thionester groups (CS.OR)

$$\delta(C{=}S) = 1.75[\delta(C{=}O)]-79.70$$

where δ(C=O) is the ^{13}C shift of the corresponding oxygen ester (CO.OR).

The total absence of (225) from the product mixture led to the proposal that the conversion proceeded by reaction at the ester carbonyl followed by reaction at the amide carbonyl. This was verified by treating a sample of (226) with Lawesson's Reagent in refluxing toluene. The

only product of this reaction was (227).

Isolation of (228) was achieved by means of preparative t.l.c. of a crude sample of (227). Its mass spectrum showed a molecular ion at m/z 249 and fragment peaks at 220 (M-Et), 188 (M-SEt), 160 (M-CO.SEt) and 116 (160-CS) thus implying the presence of an ethylthio-group and a ring thiocarbonyl, and verifying the compound as (228).

EXPERIMENTAL

INSTRUMENTAL AND GENERAL TECHNIQUES

Melting points of new compounds were obtained on a Gallenkamp variable temperature apparatus and are uncorrected.

Microanalyses for carbon, hydrogen and nitrogen were performed on a Carlo-Erba elemental analyser operated by Mrs. E. McDougall.

Infra red spectra were recorded on a Perkin Elmer 781 spectrophotometer. Solids were run as nujol mulls and liquids as thin films on sodium chloride plates. All characteristic maxima are quoted with reference to the polystyrene peak at 1603 cm^{-1}.

Proton nuclear magnetic resonance spectra were recorded on a Jeol JNM PMX60SI spectrometer (operating at 60 MHz) for routine identification and on Bruker WP-80 (80 MHz) or WP-200 (200 MHz) instruments operated by Miss H. Grant and Mr. J.R.A. Millar. High resolution and N.O.E. spectra were obtained on a Bruker WH-360 (360 MHz) operated by Dr. I.H. Sadler and Dr. D. Reed. Chemical shift values were recorded on the δ scale in p.p.m. relative to tetramethylsilane as internal standard (δ = 0). Unless otherwise stated, the solvent used was deuteriochloroform.

Mass spectra were obtained on a Kratos MS50TC (for all accurate mass measurements and for FAB spectra) an A.E.I. MS902 or a V.G. MM12F spectrometer by Mr. A. Taylor or

Miss E. Stevenson.

Alumina for column chromatography was either type UG, supplied by Laporte Industries, or Fluka neutral Type 507C and was generally deactivated with water (6% w/w) before use. Silica for column chromatography was Merck Kieselgel 60 (230-400 mesh ASTM) and for dry flash chromatography was Fluka Kieselgel GF 254.

Thin layer chromatography plates, both analytical and preparative were 0.5 mm thick and used Fluka Kieselgel GF 254 with pre-mixed fluorescent indicators. The components were observed under ultraviolet light at 254 and 366 nm or by staining with iodine.

Organic extracts were dried over anhydrous magnesium sulphate.

Commercially available solvents were used without further purification unless otherwise indicated. Dry tetrahydrofuran was prepared by refluxing with sodium metal under an atmosphere of nitrogen in the presence of benzophenone to indicate dryness and lack of peroxides. This was distilled onto freshly activated molecular sieve (type 4A). Dry ether was prepared by the addition of fresh sodium wire to the solvent. All petroleum ethers and ethyl acetate were distilled and dried before use. Ether refers to diethyl ether.

ABBREVIATIONS AND SYMBOLS

b.p.	boiling point
m.p.	melting point
decomp.	decomposition
t.l.c.	thin layer chromatography
n.m.r.	nuclear magnetic resonance
^{1}H	proton n.m.r.
^{13}C	carbon-13 n.m.r.
s; d; t	singlet; doublet; triplet
q; m	quartet; multiplet
quat.	quaternary carbon
J	coupling constant (in Herz)
δ	chemical shift
br.	broad
ν	wavenumber (cm^{-1})
M^{+}	mass of molecular ion
m/z	mass to charge ratio
h; min.	hours; minutes
M	mol dm^{-3}
I.R.	infra red

SYNTHESIS OF [1,2,4]-DITHIAZOLO[3,4,5-*de*]QUINOLIZINIUM PERCHLORATE (30)

Cyclopalladation of Quinolizine-4-thione (29)

Quinolizine-4-thione was synthesised according to the method of Van Allan and Reynolds[39] from quinolizin-4-one (57). Its suitability as a ligand for cyclopalladation had been investigated by O'Neil[15] who found that dilute solutions (*ca.* 0.015 M) were required to effect the desired reaction. In this work it was found, in addition, that a slight molar excess of quinolizine-4-thione was required. This observation was consistent with the mechanism proposed by O'Neil for this conversion.

To a stirred solution of quinolizine-4-thione (3.760 g, 0.023 mol) in methanol (1020 ml) was added dropwise a solution of sodium tetrachloropalladate (6.177 g, 0.021 mol) in methanol (520 ml). A deep red solution formed initially, which became lighter in colour with the simultaneous precipitation of an orange/brown solid. After stirring at room temperature for 2h it was heated under reflux for 7h and the suspension became yellow/ orange in colour. The solid was removed by filtration, washed with water, ethanol and ether, and dried *in vacuo* yielding di-μ-chloro-bis(4-thioxo-quinolizin-6-yl)dipalladium(II)(31),(92%), m.p. > 350°C.

ANALYSIS: Found C,35.50%; H,1.91%; N,4.60%.

Calc. C,35.80%; H,2.0%; N,4.60%.

I.R. SPECTRUM: ν_{max} 1620,1585,1560,1290,1225, 1210, 1170,1125,800,750 cm^{-1}

Bridge-splitting Reaction of Di-μ-chloro-bis(4-thioxo-quinolizin-6-yl)dipalladium(II) (31)

To a stirred suspension of the chloride-bridged dimer (31) (3.940 g, 6.53 mmol) in dimethylformamide (250 ml) was added a solution of sodium di-isopropyldithiocarbamate (2.682 g, 0.013 mol) in dimethylformamide (20 ml). This was stirred for 5h at room temperature, the solvent removed under high vacuum and the yellow/brown residue chromatographed on alumina (200 g). Elution with dichloromethane afforded 4-thioxoquinolizin-6-yl(N,N-di-isopropyldithiocarbamato)palladium(II) (32) as a yellow/orange solid (86%), m.p. 165-167°C (lit.[15] 165-168°C), crystallising from benzene as a benzene solvate, m.p. 125-127°C (lit.[15] 117-118°C).

I.R. SPECTRUM: ν_{max} 1610, 1560, 1340, 1200, 1150, 1040, 800, 790, 725, 690 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ7.77,[dd,($J_{7,8}$=7.8 Hz,$J_{7,9}$=1.4 Hz)1H,H-7];

δ7.61,[t,($^3J_{H,H}$=7.8 Hz)1H,H-8];

δ7.53,[m,3H,H-1,2,3];

δ7.37,[dd,($J_{9,8}$=7.9 Hz,$J_{9,7}$=1.5 Hz)1H,H-9];

δ5.3-4.3,[br,2H,methine protons];

δ1.50,[s,br,12H,isopropyl CH_3].

MASS SPECTRUM: m/z 442(M^+,Pd isotope pattern),

266($M-R_2NCS_2$),160(quinolizine-4-thione).

Synthesis of [1,2,4]-Dithiazolo[3,4,5-*de*]quinolizinium Perchlorate (30)

To a solution of di-*N*-morpholinyl disulphide (0.570 g, 2.42 mmol) in dichloromethane (10 ml) was added a solution of chlorine (2.4 mmol) in carbon tetrachloride (2 ml). This was stirred at ambient temperature before the dropwise addition of a solution of 4-thioxoquinolizin-6-yl(N,N-di-isopropyldithiocarbamato)palladium(II) (32), (0.504 g, 1.14 mmol) in dichloromethane (25 ml). The reaction mixture was stirred overnight at room temperature and the resultant red solid removed by filtration, resuspended in dichloromethane (15 ml) and a few drops of pyridine (or dimethyl sulphide) added. After vigorous stirring, the solution was placed in the freezer. Filtration yielded a gummy red solid which on dissolution in acetic acid and treatment with perchloric acid yielded the perchlorate salt (30) as red crystals (53%), m.p. 295°C (decomp.) (lit.[15] decomp. 300-305°C).

ANALYSIS: Found C,37.0%; H,2.04%; N,4.69%

Calc. C,37.05%; H,2.06%; N,4.80%.

I.R. SPECTRUM: ν_{max} 1630,1595,1560,1310,1235,1225,1140, 1100-1000 br,820,780,760,620 cm^{-1}.

MASS SPECTRUM: m/z 192(M^+),160,117.

REACTIONS OF [1,2,4]DITHIAZOLO[3,4,5-*de*]QUINOLIZINIUM PERCHLORATE (30)

Reaction of (30) with Formamidine

To a solution of (30) (0.023 g, 0.079 mmol) in acetonitrile (5 ml) under nitrogen was added formamidine acetate (0.012 g, 0.115 mmol) in acetonitrile (1 ml) as a suspension. This was heated and to it was added trimethyl phosphite (0.010 g, 0.081 mmol) in acetonitrile (1 ml). Heating under reflux for 8h resulted in a green solution, concentration of which gave a dark oil which was subjected to preparative t.l.c. Elution with dichloromethane/ethyl acetate (2:1) yielded quinolizine-4-thione (40%) identified by comparison of infra red, proton n.m.r. and mass spectra. None of the other materials evident on t.l.c. was isolated in a large enough amount for n.m.r. nor did they give molecular ions under mass spectrometric conditions.

Reaction of (30) with Acetamidine

To a solution of (30) (0.060 g, 0.206 mmol) in acetonitrile (8 ml) under nitrogen was added tri-*n*-butyl-phosphine (0.042 g, 0.207 mmol) in acetonitrile (2 ml). No change in the colour of the solution was observed but t.l.c. indicated the formation of a yellow substance (Rf 0.82) and an orange substance (Rf 0.64). No attempt was made to isolate or identify these. To this solution was

added acetamidine hydrochloride (0.020 g, 0.212 mmol) and potassium carbonate (0.029 g, 0.217 mmol) as a suspension in acetonitrile (2 ml). After being heated under reflux for 20h, the solution had become green and was concentrated under vacuum and subjected to preparative t.l.c., eluting with dichloromethane/methanol (5%). Ten very narrow, but intensely-coloured bands were observed. The major, blue band (Rf 0.25) was eluted from the silica using dichloromethane/methanol (1:1) and yielded tri-*n*-butylphosphine oxide (32%), m/z 218(M^+),168. The other products as evident on t.l.c. were isolated only in trace amounts and could not be identified.

Reaction of (30) with Sodium Dithionite

To a solution of (30) (0.114 g, 0.391 mmol) in water (80 ml, distilled) at ice bath temperature under nitrogen was added dropwise a solution of sodium dithionite (0.150 g, 0.781 mmol) in sodium hydroxide solution (2 ml, 0.25 M), resulting in the formation of a yellow/brown precipitate. To the suspension was added iodomethane (0.054 g, 0.380 mmol) in dichloromethane (5 ml). After stirring for 2h, the precipitate dissolved and the organic layer became deep red. This was separated, dried over anhydrous magnesium sulphate and the volume reduced on a rotary evaporator. The concentrated residue was subjected to preparative t.l.c., eluting with dichloromethane/ethyl acetate (5%). This afforded quinolizine-4-thione (30%) as

a by-product, and 6-methylthioquinolizine-4-thione (37) as an orange/red solid (31%), m.p. 115-117°C.

ANALYSIS: Found C,57.67%; H,4.45%; N,6.40%

Calc. C,57.97%; H,4.35%; N,6.76%.

I.R. SPECTRUM: ν_{max} 1615,1550,1310,1300,1255,1205,1155, 1145,965,900,875,860,795 cm^{-1}.

^1H n.m.r. (360 MHz):

δ7.77,[dd,($J_{3,2}$=8.2 Hz,$J_{3,1}$=1.5 Hz)1H,H-3];

δ7.30,[dd,($J_{2,3}$=8.2 Hz,$J_{2,1}$=7.5 Hz)1H,H-2];

δ7.26,[dd,($J_{8,7}$=8.6 Hz,$J_{8,9}$=7.2 Hz)1H,H-8];

δ7.17,[dd,($J_{7,8}$=8.6 Hz,$J_{7,9}$=1.5 Hz)1H,H-7];

δ7.10,[dd,($J_{9,8}$=7.2 Hz,$J_{9,7}$=1.5 Hz)1H,H-9];

δ6.99,[dd,($J_{1,2}$=7.6 Hz,$J_{1,3}$=1.5 Hz)1H,H-1];

δ2.46,[s,3H,methyl protons].

MASS SPECTRUM: m/z 207(M^+),192,160

ACCURATE MASS: Found M^+ 207.0192 $C_{10}H_9NS_2$

Requires M 207.0186

Reaction of 6-Methylthioquinolizine-4-thione (37) with Methyl Iodide

To a warm solution of the title compound (0.007 g, 0.034 mmol) in ether (10 ml) was added excess methyl iodide and the mixture warmed for a further few minutes. On cooling, the orange solution became yellow and a yellow precipitate was evident. The flask was placed in the fridge overnight to effect complete precipitation. Evaporation of the solvent led to the isolation of

4,6-bis(methylthio)quinolizinium iodide (38), (96%, crude).

MASS SPECTRUM:(FAB) m/z 222(M^+)

ACCURATE MASS:(FAB) Found M^+ 222.0411 $C_{11}H_{12}NS_2$

Requires M 222.0411.

Due to lack of time and material, this product was not purified, nor further characterised at this stage.

Reaction of 4,6-Bis(methylthioquinolizinium)iodide (38) with Formamidine

To a solution of the title compound (0.010 g, 0.029 mmol) in acetonitrile (2 ml) was added formamidine acetate (0.039 g, 0.038 mmol) as a suspension in acetonitrile (1 ml). The yellow solution was heated under gentle reflux under nitrogen for 24h, causing a colour change to green. T.l.c. at this stage indicated the formation of a blue material at Rf 0.70 in dichloromethane/ ethanol (5%). The reaction mixture was partially concentrated under vacuum and subjected to preparative t.l.c., eluting with the aforementioned solvent system. On removal from the silica, the blue band yielded 1,3-diaza[3.3.3]cyclazine (21), (92%), m.p. 168-170°C.

ACCURATE MASS:(FAB) Found $(M+1)^+$ 170.0718 $C_{10}H_8N_3$

Requires (M+1) 170.0718.

I.R. SPECTRUM: (solution in dichloromethane) ν_{max} 1635, 1620,1560,1465,1400,1325,1230,1200,1040,900,870,820 cm^{-1}.

U.V. SPECTRUM: (ethanol) λ_{max} at 233(ε 14500),258(ε 20483),352(ε 14331), 643(ε 273),704(ε 321),779(ε 169).

^{1}H n.m.r. (200 MHz):

δ6.06,[t,($^3J_{H,H}$=8.2 Hz)2H,H-5,8];

δ5.88,[s,1H,H-2];

δ5.10,[dd,($^3J_{H,H}$=8.5 Hz,$^4J_{H,H}$=1.3 Hz)2H,H-4,9];

δ4.61,[dd,($^3J_{H,H}$=7.9 Hz,$^4J_{H,H}$=1.4 Hz)2H,H-6,7].

MASS SPECTRUM:(FAB) m/z 170(M+1)

Reaction of (30) with Ethyl Cyanoacetate

To a solution of (30) (0.050 g, 0.172 mmol) in acetonitrile (5 ml) under argon in a Schlenk tube was added a solution obtained by reaction of ethyl cyanoacetate (0.020 g, 0.177 mmol) with sodium hydride (0.005 g, 0.208 mmol) in acetonitrile (2 ml). The combined solution was stirred and heated under argon for 3h, during which, t.l.c. showed the appearance of a green spot. The concentrated reaction mixture was subjected to dry flash column chromatography under argon, eluting with dichloromethane/ethyl acetate (5%). Two fast moving bands, one red, one green could not be completely separated and were collected together. The proton n.m.r. spectrum of the mixture showed a complex signal pattern in the region δ8.01-7.25 and a separate set of signals in the region δ6.25-4.73. This latter set was consistent with two AMX systems, i.e. showed two overlapping triplets between δ6.25-5.96, the coupling constants of which could

not be precisely determined due to second order effects, and four partially-overlapping doublets of doublets, each displaying one large (*ortho*) and one small (*meta*) coupling constant.

In an effort to separate these two components, the mixture was again subjected to dry flash chromatography under argon. However, only trace amounts of separated compounds were obtained and they could not be characterised by n.m.r. The original products were believed to have decomposed on prolonged exposure to silica.

The experiment was repeated in dried and degassed tetrahydrofuran, resulting in a green solution which was partially concentrated and subjected to dry flash chromatography under argon, eluting with dichloromethane and yielding a blue and a yellow fraction.

The yellow material showed a complicated signal pattern between δ8.10-7.18 in its proton n.m.r. spectrum and mass spectroscopic peaks at m/z 426 (Pd isotope pattern),287,160. This latter evidence suggested that compound (149) was present. Comparison of the proton n.m.r. spectrum with that of (149) indicated the possible presence of (149) in addition to some other substance. The sensitivity of this substance to air prevented its identification.

N.m.r. and mass spectrometric data on the blue component were inconclusive but offered no evidence for

the formation of any of the species predicted in Fig. (35).

Reaction of (30) with Diethyl Malonate

In a procedure analogous to that for ethyl cyanoacetate, (30) (0.040 g, 0.137 mmol) in dried and degassed tetrahydrofuran (2 ml) was treated with a solution of diethyl malonate (0.023 g, 0.144 mmol) and sodium hydride (0.004 g, 0.167 mmol). The combined solution was stirred at ambient temperature, then brought to reflux under argon for 2h. An orange/brown solid formed and was removed by filtration. Its mass spectrum showed peaks at m/z 426,160 - consistent with the presence of compound (149). However the aromatic signals in the proton n.m.r. spectrum were inconsistent with those of (149) and the identity of the solid was not determined.

The soluble portion of the reaction mixture was concentrated and gave a proton n.m.r. spectrum exhibiting signals in the region δ8.25-7.25 and δ5.75-4.95. However, sensitivity of this material to air prevented separation or identification of the two components.

Reaction of (30) with Divalent Metal Ions

This reaction was carried out for Pd(II) and Ni(II) according to the general procedure described as follows.

To a chilled (0°C) aqueous solution of (30) under a nitrogen atmosphere, was added dropwise an aqueous

solution of sodium borohydride and 0.5 mol equiv. of M(II). The precipitate formed was dried and characterised.

Pd(II): The metal ion was supplied as a methanolic solution of sodium tetrachloropalladate. Precipitation was complete after 1h and the red/brown solid was separated in 98% yield by centrifuge.

MASS SPECTRUM: m/z 426(M-2S,Pd isotope pattern),256(S_8), 224(S_7) etc.

This solid was sublimed at 210°C/0.8 mm, forming a yellow sublimate and a dark residue. T.l.c. indicated the sublimate to be quinolizine-4-thione and the residue to have decomposed.

Ni(II): The metal ion was supplied as an aqueous solution of nickel chloride hexahydrate. Precipitation was complete after 3h and the red/brown solid was removed by filtration, washed with ethanol and ether and dried *in vacuo* giving bis(4-thioquinolizin-6-ylthio-S,S)nickel(II) (33) in quantitative yield, m.p. 200-204(decomp.).

MASS SPECTRUM: m/z 378(M-2S,Ni isotope pattern),256(S_8), 224(S_7) etc.,160.

The red/brown solid (33) was sublimed at 190°C/0.1 mm to effect sulphur extrusion, forming a pale yellow sublimate and a dark residue. T.l.c. indicated the sublimate to be molecular sulphur and a trace of quinolizine-4-thione (29). Preparative t.l.c. of the residue gave two compounds at Rf 0.67 (red) and Rf 0.78

(brown). The red solid was identified as bis(4-thioxoquinolizin-6-yl-S)nickel(II) (34) (90%), m.p. > 335°C on the basis of the following spectroscopic data.

ACCURATE MASS: Found M^+ 377.9792 $C_{18}H_{12}N_2S_2Ni$

Requires M 377.9795.

I.R. SPECTRUM: ν_{max} 1610,1550,1300,1280,1220,1195,1155, 1110,1050,795 cm^{-1}.

^1H n.m.r. (600 MHz)

δ8.21,[dd,(J values show second order effects)1H,H-7];

δ7.75,[dd,($J_{3,2}$=7.7 Hz,$J_{3,1}$=1.3 Hz)1H,H-3];

δ7.54,[t,($^3J_{H,H}$=7.8 Hz)1H,H-2];

δ7.48,[dd,($J_{9,8}$=8.3 Hz,$J_{9,7}$ shows second order effects)1H, H-9];

δ7.46,[dd,($J_{8,9}$=8.3 Hz,$J_{8,7}$ shows second order effects)1H, H-8];

δ7.30,[dd,($J_{1,2}$=7.9 Hz,$J_{1,3}$=1.3 Hz)1H,H-1].

MASS SPECTRUM: m/z 378(M^+,Ni isotope pattern),160.

The brown solid showed mass spectrometric peaks at m/z 410 and 394, consistent with the incorporation of two and one oxygen atoms respectively into the aforementioned red compound. The brown compound was believed to have been formed by aerial oxidation of the red compound on exposure to silica. In subsequent reactions, therefore, the sulphur extrusion reaction was effected in refluxing *o*-dichlorobenzene for 2h and the solid recovered by evaporation was subjected to Soxhlet extraction with chloroform. The product was obtained by slow

crystallisation from the chloroform extracts, without the necessity for purification by t.l.c. Formation of the oxidised product was thereby avoided.

Reaction of Bis(4-thioquinolizin-6-yl-S)nickel(II) (34) with $Co(TFA)_3$

To a stirred solution of the title complex (0.029 g, 0.077 mmol) in chloroform at room temperature was added cobalt tris(trifluoroacetate) [0.034 g, 0.077 mmol Co(III)]. The red solution turned to a yellow/orange suspension after 2 min. T.l.c. at this stage indicated consumption of starting material. A further mol. equiv. of oxidant was added and the suspension stirred for 1h at room temperature. The solid was removed by filtration, dried *in vacuo* (0.046 g) and analysed by mass spectrometry.

MASS SPECTRUM: m/z 331,329,253,251,222,220,187,185,160, 149.

The identity of this solid remained undetermined.

The soluble portion of the reaction mixture was subjected to preparative t.l.c., eluting with dichloromethane/ethyl acetate (4%) and giving two bands (Rf 0.90 and Rf 0.15). The fast-moving, yellow material was identified as quinolizine-4-thione (29), (10%) by mass spectrometry, (m/z 161,160,117) and the slow, fluorescent material exhibited peaks at m/z 222,220,187,185,160,149, i.e. very similar to those exhibited by the solid portion

of the reaction mixture, and could not be identified.

Repetition of the experiment involved treatment of the title complex (0.041 g, 0.108 mmol) with 1 mol. equiv. of Co(III) and led to the same colour change. The solid (0.055 g) was removed by filtration, dried and examined by mass spectrometry, exhibiting peaks at m/z 378,333,331, 218,207,161,117, consistent with the presence of oxidised starting material.

Once again, the soluble portion was subjected to preparative t.l.c., eluting with dichloromethane/ethyl acetate (4%). However, the only material identified was quinolizine-4-thione (5%), m/z 161,117.

SYNTHESIS OF 6,6'-DISUBSTITUTED-2,2'-BIPYRIDINES

Synthesis of 6-Bromo-2-picoline (155)

Method A

To a stirred solution of 6-amino-2-picoline (54.304 g, 0.503 mol) in 48% hydrobromic acid (283.1 g, 1.677 mol) was added liquid bromine (232.5 g, 1.453 mol) dropwise over 1.5h producing a coarsely granular, red/brown reaction mixture. An aqueous solution (126 ml) of sodium nitrite (87.139 g, 1.269 mol) was added slowly over 1.5h and the reaction mixture lost its granular appearance. Bromine gas produced at this stage was led into water. The reaction mixture was neutralised with aqueous sodium hydroxide and extracted into dichloromethane. Residual bromine was removed from the organic layer by treatment with a saturated aqueous solution of sodium sulphite. Following neutralisation the organic layer was separated, dried over anhydrous magnesium sulphate and the concentrated reaction mixture distilled under reduced pressure (94-100°C/16 mm). The distillate contained mono-, di-, and tri-bromo picolines. The dibromo compound was a white solid, m.p. 34-36°C and could be removed by filtration.

I.R. SPECTRUM: ν_{max} 1560,1540,1460,1210,1140,1125,1030, 820 cm^{-1}.

^1H n.m.r. (200 MHz)

δ7.59,[dq,($J_{4,5}$=8.3 Hz,$^5J_{H,H}$=0.4 Hz)1H,H-4];

δ7.17,[dq,($J_{5,4}$=8.3 Hz,$^{6}J_{H,H}$=0.7 Hz)1H,H-5];

δ2.62,[s,3H,methyl protons].

N.O.E. SPECTRUM (360 MHz):

Irradiation at the frequency corresponding to the signal at δ2.62 caused no enhancement of the remaining signals. the compound was thus identified as 3,6-dibromo-2-picoline (156).

MASS SPECTRUM: m/z 253(M^{+},2x^{81}Br),251(M^{+}^{79}Br,^{81}Br), 249(M^{+},2x^{79}Br),172,170(M-Br),91(M-2Br).

Distillation of the remaining liquid allowed the more volatile monobromo product (155) to be obtained in a pure state as a clear liquid (44%) b.p. 44-48°C/0.5 mm.

I.R. SPECTRUM: ν_{max} 1590,1560,1450,1410,1260,1240,1170, 1130,1095,1040,1005,850,790,675 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ7.27,[t,($^{3}J_{H,H}$=7.7 Hz)1H,H-4];

δ7.11,[dm,1H,H-3];

δ6.94,[dm,1H,H-5];

δ2.36,[s,3H,methyl protons].

MASS SPECTRUM: m/z 173(M^{+},^{81}Br),171(M^{+},^{79}Br),92(M-Br).

The tribromo compound remained in the distillation residue and was not isolated. Its presence in the original reaction mixture was verified by proton n.m.r. spectrometry, indicating two singlets at δ7.87 and 2.69.

In an effort to reduce the polybromination, in later experiments the liquid bromine was added over five minutes to reduce the contact time with 6-amino-2-picoline and

thereby the extent of electrophilic bromination prior to diazotisation. However, substantial amounts of the dibromo compound were still produced, as verified by proton n.m.r. spectrometry.

Method B : Modified Sandmeyer Reaction

To a solution of copper(I) bromide (64.531 g, 0.457 mol) in HBr (170ml, 48%) at -10°C was added 6-amino-2-picoline (48.475 g, 0.449 mol) in HBr (50 ml, 48%) over a 10 minute period. The mixture was stirred at -10°C for 15 min. forming a viscous suspension. An aqueous solution (100 ml) of sodium nitrite (100.30 g, 1.454 mol) was added dropwise over two hours and the resulting mixture treated with 0.88 NH_3 to complex out the residual copper as a blue solid. This was removed by filtration and the dark filtrate extracted into dichloromethane dried and concentrated, yielding a brown oil which solidified on standing. Distillation (170°C/20 mm) yielded a mixture of 6-methyl-2-pyridone (162) and its 3-bromo analogue (163) as a white solid.

^{1}H n.m.r. (200 MHz): (6-methyl-2-pyridone)

δ11.5,[s,br,NH];

δ7.34,[dd,($J_{4,5}$=6.7 Hz,$J_{4,3}$=9.1 Hz)1H,H-4];

δ6.37,[d,($J_{3,4}$=9.1 Hz)1H,H-3];

δ6.04,[d,($J_{5,4}$=6.9 Hz)1H,H-5];

δ2.32,[s,3H,methyl protons].

The presence of the 3-bromo analogue was established by the signals at δ7.46,[d,($J_{4,5}$=9.5 Hz)H-4]; δ6.25,

[d,($J_{5,4}$=9.5 Hz)H-5]; and a trace amount of the 5-bromo isomer was identified by two doublets δ7.61, [d,($J_{4,3}$=7.4 Hz)H-4]; δ5.89,[d,($J_{3,4}$=7.4 Hz)H-3].

MASS SPECTRUM: m/z 189,187(M^+,bromo analogues),109[M^+ for (162)].

Method C : Two Stage Process

According to the method of Adams and Schrecker[85], a solution of 6-amino-2-picoline (10.748 g, 0.099 mol) in a cold mixture of concentrated sulphuric acid (11 ml) and water (65 ml) was placed in an ice-salt bath. With vigorous stirring, an aqueous solution (18 ml) of sodium nitrite (7.400 g, 0.107 mol) was added dropwise over 45 min. The temperature was maintained below 0°C during addition and whilst stirring for a further hour, resulting in an off-white precipitate. The reaction temperature was then raised to 90°C for 1h. After cooling, the solution was made alkaline by the addition of anhydrous potassium carbonate (27.110 g, 0.196 mol) and the mixture evaporated to dryness. The residue was powdered and extracted exhaustively with boiling benzene yielding off-white crystals of 6-methyl-2-pyridone (162),(88%),m.p. 157-159°C (lit.[85] 158-159°C).

I.R. SPECTRUM: ν_{max} 1685,1625,1560,1220,1180,1090,1060, 1040,1010,950,880,810 cm^{-1}.

^{1}H n.m.r. (80 MHz): as for Method B

MASS SPECTRUM: m/z 109(M^+),81(M-CO).

6-Methyl-2-pyridone (1.460 g, 0.013 mol) obtained in

this way was treated with phosphoryl bromide (1.50 g, 5.2 mmol) and the mixture stirred with protection from moisture at 170°C for 6h. The resultant dark brown solution solidified on cooling and was taken up in water (30 ml) and separated into ether, yielding a light brown oil. This was distilled (50°C/0.4 mm) to give 6-bromo-2-picoline (43%). All spectra were in accordance with those obtained *via* Method A.

The Synthesis of 6,6′-Dimethyl-2,2′-bipyridine (41)

Method A

According to the method of Newkome[65], a mixture of 6-bromo-2-picoline (24.399 g, 0.142 mol), sodium formate (14.670 g, 0.216 mol), 5% palladium charcoal (0.86 g), benzyltriethylammonium chloride (5.76 g, 0.022 mol), 32% sodium hydroxide (w/w 30 ml) and water (120 ml) were heated under reflux for 48h, with the addition of further sodium formate (3.70 g, 0.054 mol) and palladium charcoal (0.64 g) after 8h and 16h. The cooled reaction mixture was filtered through Celite, extracted in dichloromethane and dried over anhydrous magnesium sulphate. Evaporation of the solvent afforded a brown crystalline product which was recrystallised from petroleum ether 40/60 yielding 6,6′-dimethyl-2,2′-bipyridine (41) (33%) as a white solid, m.p. 90-91°C (lit.[84] 89-90°C).

I.R. SPECTRUM: ν_{max} 1580,1250,1150,1080,1030,995,780, 635 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ8.16,[d,($J_{3,4}$=7.7 Hz)1H,H-3];

δ7.67,[t,($^3J_{H,H}$=7.7 Hz)1H,H-4];

δ7.14,[d,($J_{5,4}$=7.7 Hz)1H,H-5];

δ2.62,[s,3H,methyl protons].

MASS SPECTRUM: m/z 184(M^+),169(M-CH_3),154(M-2CH_3), 143(M-H_3CCN),92($\frac{1}{2}$M).

Method B

An aqueous slurry of Raney nickel was warmed gently under vacuum until the evolution of water vapour was complete, then heated to 50°C for a further hour to ensure total degassing of the catalyst. An atmosphere of nitrogen was admitted and the weight of the catalyst noted (1.063 g). A solution of 6-bromo-2-picoline (1.507 g, 8.76 mmol) in sodium-dried, absolute toluene (18 ml) was added *via* syringe and the mixture heated under reflux for 24h. The resultant purple solid was removed and stirred with warm water (40°C) until the pale violet suspension turned green. This was filtered and the solid washed with chloroform. The filtrate was separated and reduced under vacuum yielding 6,6'-dimethyl-2,2'-bipyridine (41) as an off-white solid (22%) with spectra in accordance with those previously reported.

Method C

According to the method of Tiecco and Testaferri[88], to a deep blue/green solution of nickel(II) chloride hexahydrate (5.692 g, 0.024 mol) and triphenylphosphine

(25.066 g; 0.096 mol) in dimethylformamide (120 ml) under nitrogen at 50°C was added zinc powder (1.552 g, 0.024 mol). Within 15 min. the solution had become brown and was stirred at 50°C for 1h, before the addition of 6-bromo-2-picoline (4.21 g, 0.024 mol) in dimethyl-formamide (15 ml), producing a mild exothermic reaction. T.l.c. indicated consumption of the starting material after 3h. The mixture was poured onto dilute ammonia solution (500 ml) and extracted with chloroform. The organic phase was then acidified with dilute HCl to remove the product into the aqueous layer on account of its basicity. The organic phase, now containing mainly triphenylphosphine as determined by t.l.c., was concentrated and could be recycled. The acidic aqueous phase was made alkaline with aqueous sodium hydroxide solution, extracted into chloroform, dried and concentrated *in vacuo* to give an off-white solid which was sublimed, yielding 6,6'-dimethyl-2,2'-bipyridine (41),(16%). All spectra were in accordance with those recorded in Method A.

Method D

According to the work of Haginiwa and Higuchi[66], 2-picoline (5.591 g, 0.060 mol), 2-picoline-N-oxide (6.216 g, 0.057 mol) and 5% palladium-charcoal (1.966 g) were heated under reflux for 48h, until t.l.c. indicated consumption of starting materials. The reaction mixture was cooled, dichloromethane (30 ml) was added and the

mixture filtered through Celite, dried and concentrated under vacuum. The resultant solid was subjected to kugelröhr distillation yielding the desired 6,6′-dimethyl-2,2′-bipyridine (41), (10%). All spectra were in accordance with those reported for Method A.

This method (D) was repeated using various activities of palladium-charcoal catalyst. However, none was as successful as the 5% sample described above.

Attempted Synthesis of 6,6′-Bis(chloromethyl)-2,2′-bipyridine (42)

Method A

Newkome *et al.*[64] claimed to have effected this synthesis in 70% yield from 6,6′-dimethyl-2,2′-bipyridine (41) by treatment with N-chlorosuccinimide.

In an attempt to repeat this, a solution of 6,6′-dimethyl-2,2′-bipyridine (1.800 g, 9.780 mmol) in carbon tetrachloride (50 ml) was treated with N-chlorosuccinimide (2.896 g, 0.022 mol) and benzoyl peroxide (25 mg) and the solution was heated under reflux for 24h. After this time, white crystals of succinimide had been precipitated and were removed by filtration. The filtrate was washed with saturated aqueous solutions of sodium carbonate and sodium chloride. The organic phase was dried and concentrated under vacuum, yielding a yellow solid (1.792 g) containing unreacted NCS (as tested for using moist starch iodide paper) as well as 6,6′-bis-

(chloromethyl)-2,2'-bipyridine (42) and starting material in a ratio 4:10 (as ascertained by proton n.m.r. spectroscopy). This yellow solid was subjected to a further 24h reflux in carbon tetrachloride in the presence of fresh benzoyl peroxide, and the work-up procedure repeated yielding a yellow crystalline solid (1.339 g) m.p. 118-128°C. The proton n.m.r. spectrum indicated this solid to be a mixture of product and starting material in relative proportions 10:4 and overall un-isolated yields of 38% and 12% respectively. These two components could be separated chromatographically on alumina (6% deactivated) eluting with cyclohexane/ether (15%) and the 6,6'-bis(chloromethyl)-2,2'-bipyridine (42) recrystallised from cyclohexane (20% isolated yield), m.p. 156-158°C (lit.[64] m.p. 157-158°C).

I.R. SPECTRUM: ν_{max} 1585,1570,1260,1080,995,815,775, 695 cm^{-1}.

^1H n.m.r. (80 MHz):

δ8.38,[dd,($J_{3,4}$=7.8 Hz,$J_{3,5}$=1.1 Hz)1H,H-3];

δ7.83,[t,($^3J_{H,H}$=7.7 Hz)1H,H-4];

δ7.48,[dd,($J_{5,6}$=7.7 Hz,$J_{5,3}$=1.1 Hz)1H,H-5];

δ4.73,[s,2H,methylene protons];

MASS SPECTRUM: m/z 256(M^+,2x^{37}Cl),254(^{35}Cl,^{37}Cl), 252(2x^{35}Cl),219,217(M-Cl).

Method B

To a solution of 6,6'-dimethyl-2,2'-bipyridine (0.493 g, 1.86 mmol) in chloroform (10 ml) was added

benzamide (0.011 g, 0.091 mmol) and the mixture brought to reflux for 1h before the addition of trichloroisocyanuric acid (0.356 g, 1.531 mmol) in small portions to the refluxing mixture. Refluxing was maintained for a further 5h and thereafter the reaction was monitored by t.l.c. However, despite the excess of chlorinating reagent, the major component of the mixture was starting material. This was verified by the proton n.m.r. spectrum of the crude product obtained via alkaline work-up of the reaction mixture.

The Synthesis of 6,6′-Dibromo-2,2′-bipyridine (167)

This was obtained in 60% yield according to the method of Parks *et al.*[70].

The Synthesis of 6,6′-Diformyl-2,2′-bipyridine (168)

This was obtained in 60% yield according to the method of Parks *et al.*[70].

The Synthesis of 6,6′-Diethynyl-2,2′-bipyridine (169)

To a stirred suspension of 6,6′-dibromo-2,2′-bipyridine (0.738 g, 2.350 mmol) in diethylamine (5.3 ml) was added 2-methyl-but-3-yn-2-ol (0.444 g, 5.286 mmol), bis(triphenylphosphine)palladium(II) dichloride (42 mg) and copper(I) iodide (21 mg) as a suspension in benzene (2 ml). This was stirred at ambient temperature for 1½h, after which time, t.l.c. indicated complete consumption of

starting material. The concentrated reaction mixture was separated into ether from water, and the organic phase yielded crude product which could be recrystallised from cyclohexane/ethyl acetate (10%) to give 6,6'-bis(3-hydroxy-3-methylbut-1-ynyl)-2,2'-bipyridine (171),(93%), m.p. 156-158°C.

ANALYSIS: Found C,74.41%; H,6.21%; N,8.52%.

Calc. C,75.00%; H,6.25%; N,8.75%.

I.R. SPECTRUM: ν_{max} 3400-3100(OH stretch),1565,1290,1210, 1170,1150,970,960,810 cm^{-1}.

^1H n.m.r. (80 MHz):

δ8.37,[dd,($J_{5,4}$=7.9 Hz,$J_{5,3}$=1.2 Hz)1H,H-5];

δ7.74,[t,($^3J_{H,H}$=7.8 Hz)1H,H-4];

δ7.39,[dd,($J_{3,4}$=7.7 Hz,$J_{3,5}$=1.2 Hz)1H,H-3];

δ2.20,[s,br,O-H];

δ1.65,[s,6H,methyl protons].

MASS SPECTRUM: m/z 320(M^+),305.

To a suspension of (171) (0.879 g, 2.75 mmol) thus obtained, in toluene (14 ml) was added crushed sodium hydroxide (0.360 g, 0.016 mol) and the mixture heated under reflux for 2h. At the end of this time, t.l.c. indicated consumption of starting material. The reaction mixture was diluted with toluene (10 ml) and filtered. The concentrated filtrate was taken up in dichloromethane and washed with aqueous sodium chloride solution. The organic layer was then dried over anhydrous magnesium sulphate, concentrated under vacuum and recrystallised

from toluene, yielding the light-sensitive 6,6′-diethynyl-2,2′-bipyridine (169),(67%),m.p. 180-183(decomp.).

ANALYSIS: Found C,82.33%; H,4.21%; N,13.43%.

Calc. C,82.35%; H,3.92%; N,13.73%.

I.R. SPECTRUM: ν_{max} 3280 (C≡C-stretch),1575,1560,1080, 990,800,680,640 cm^{-1}.

^1H n.m.r. (80 MHz):

δ8.46,[dd,($J_{5,4}$=7.8 Hz,$J_{5,3}$=1.3 Hz)1H,H-5];

δ7.78,[t,($^3J_{H,H}$=7.8 Hz)1H,H-4];

δ7.48,[dd,($J_{3,4}$=7.7 Hz,$J_{3,5}$=1.3 Hz)1H,H-3];

δ3.16,[s,1H,acetylenic proton].

MASS SPECTRUM: m/z 204($M^{+\cdot}$),153,152.

The Synthesis of 6,6′-Dicyano-2,2′-bipyridine (172)

Method A

To a suspension of 6,6′-dibromo-2,2′-bipyridine (0.359 g, 1.14 mmol) in dimethylformamide (10 ml) was added copper(I) cyanide (0.204 g, 2.28 mmol) and bis-(triphenylphosphine)palladium(II) dichloride (20mg). The resultant orange suspension was heated under reflux for 2-4h, forming a dark red solution. On completion of the reaction (as determined by t.l.c.) the reaction mixture was poured onto a warm solution of sodium cyanide (1.030 g, 0.021 mol) in water (15 ml), producing a grey-white solid which was filtered off. The filtrate was extracted into benzene, dried over anhydrous magnesium sulphate and concentrated *in vacuo* yielding more grey-

white solid. The solids were combined and subjected to sublimation (180°C/0.5 mm) then recrystallisation from methanol to give 6,6'-dicyano-2,2'-bipyridine (172) as colourless needles (69%) m.p. 251-254°C (lit.[71] 255°C).

I.R. SPECTRUM: ν_{max} 2240(C≡N stretch),1580,1160,1085, 990,805 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.71,[dd,($J_{5,4}$=8.1 Hz,$J_{5,3}$=1.0 Hz)1H,H-5];

δ8.04,[t,($^3J_{H,H}$=8.0 Hz)1H,H-4];

δ7.77,[dd,($J_{3,4}$=7.6 Hz,$J_{3,5}$=1.0 Hz)1H,H-3].

MASS SPECTRUM: m/z 206(M^+),180(M-CN),154(M-2CN).

Method B: From 2,2'-Bipyridine-Di-N-Oxide (174)

2,2'-Bipyridine-di-N-oxide was synthesised in 91% yield according to the method of Simpson[97].

To a solution of 2,2'-bipyridine-di-N-oxide (1.482 g, 7.88 mmol) in dimethylformamide (5 ml) was added trimethylsilyl cyanide (4.007 g, 0.014 mol) dropwise over ½h. The solution was heated under reflux for 23h and monitored by t.l.c. On completion of the reaction, the mixture was cooled, washed with sodium bicarbonate solution and separated into dichloromethane. Concentration under vacuum afforded a brown solid which was washed with methanol (2-3 ml), yielding an off-white solid. This was sublimed (180°C/0.5 mm) producing 6,6'-dicyano-2,2'-bipyridine (10%) m.p. 251-253°C (decomp.).

All spectra obtained were in accordance with those

from Method A.

TOWARDS 6,6'-BIS(QUINOLIZIN-4-ONE) (44)

Synthesis of Ethyl 2-Pyridylacetate

Method A

The method of Woodward and Kornfeld[98] led to the title compound (21%) b.p. 80-85°C/0.8 mm.

I.R. SPECTRUM: ν_{max} 1750-1720(carbonyl stretch),1595, 1570,1480,1440,1370,1340,1260(br),1160(br),1100,1035,1000, 755 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.51,[dd,($J_{6,5}$=4.8 Hz,$J_{H,H}$=0.8 Hz)1H,H-6];

δ7.61,[td,($^3J_{H,H}$=7.7 Hz,$^4J_{H,H}$=1.8 Hz)1H,H-4];

δ7.27-7.11,[m,2H,H-5 and H-3];

δ4.14,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ3.80,[s,2H,2-pyridyl CH_2];

δ1.22,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

Method B

The method of Goldberg *et al.*[99] was adapted to involve

the use of ethyl chloroformate on 2-picolyl-lithium and led to ethyl 2-pyridylacetate (14%) with spectra in accordance with those recorded for Method A.

Method C

An adaptation of the method of Vorbrüggen[96] led to the treatment of a chilled (0°C) solution of freshly-distilled pyridine-N-oxide (0.30 g, 3.16 mmol) in dry tetrahydrofuran (5 ml) under an atmosphere of nitrogen, with ethyl trimethylsilylacetate (1.007 g, 6.28 mmol), added in a dropwise manner. The clear liquid was allowed to stir at 0°C for 5 min. before the addition of tetra-*n*-butylammonium fluoride (0.091 g, 0.35 mmol).

The resulting red solution was stirred with the exclusion of air for a further 1½h. Separation into ether from water afforded a red/brown oil in low yield. Comparison of the infra red spectrum with that of pyridine-N-oxide established the oil's identity as starting material.

Method D

Adaptation of the general method of Webb[100] involved the treatment of a suspension of pyridine-N-oxide (2.011 g, 0.021 mol) and isobutyl chloroformate (2.886 g, 0.021 mol) in tetrahydrofuran (15 ml) at -50°C under an atmosphere of nitrogen, with a solution of ethoxycarbonylmethylzinc bromide [from ethyl bromoacetate (4.183 g, 0.028 mol) and zinc wool (1.870 g, 0.029 mol)]

in tetrahydrofuran (50 ml). A yellow/orange suspension was immediately produced and dissolved on stirring. The solution was then allowed to warm to room temperature and extracted into ether from water. The organic phase was dried, concentrated and distilled 75-80°C/0.7 mm, affording a small amount of isobutyl chloroformate in the distillate, as identified by its proton n.m.r. spectrum. The residue became dark red and intractable and was not amenable to chromatography.

Method E:

To a solution of recrystallised Meldrum's acid (5.681 g, 0.039 mol) in acetic anhydride (50 ml) at 0°C was added freshly distilled pyridine-N-oxide (3.751 g, 0.039 mol) in acetic anhydride (25 ml) dropwise over 1h. This caused the solution to become deep red/brown and t.l.c indicated almost total consumption of the Meldrum's acid. The reaction mixture was stirred at room temperature overnight and the solvent removed under vacuum to give a black, intractable tar which was not amenable to chromatography. Distillation of a sample of this yielded a small amount of an unidentified oil and led to extensive charring of the residue. A further sample of the intractable tar was dissolved in absolute ethanol (270 ml) and HCl gas passed through the chilled solution for 3h. This was neutralised with sodium carbonate solution, extracted into dichloromethane yielding a brown viscous oil whose proton n.m.r. and mass spectra offered no

evidence for the formation of ethyl 2-pyridylacetate.

Attempted Synthesis of Diethyl (2,2'-bipyridine-6,6'-diyl)diacetate (175)

To a solution of 6,6'-dimethyl-2,2'-bipyridine (0.252 g, 1.37 mmol) in dry tetrahydrofuran (10 ml) at -78°C under an atmosphere of nitrogen was added *n*-butyl-lithium (3.00 mmol), turning the solution dark green immediately. After warming to ambient temperature, the solution was cooled once again (-78°C) and to it added dropwise a solution of ethyl chloroformate (0.319 g, 2.94 mmol) in tetrahydrofuran (3 ml). The solution was allowed to warm to ambient temperature, extracted into dichloromethane from water and the concentrated organic phase subjected to dry flash column chromatography on silica, eluting with petroleum ether 80-100/ethyl acetate (4%). Two fractions were obtained. The first was identified as starting material (27%) from its proton n.m.r. and mass spectra. The second yielded a small amount (54 mg) of an impure material, the mass spectrum of which exhibited peaks at m/z 328[M^+ for (175)] and 283(M-OEt). The accurate mass of the former peak was in accordance with the title compound.

ACCURATE MASS: Found M^+ 328.1417 $C_{18}H_{20}N_2O_4$

Requires M 328.1419

In the light of the poor yield and purity of the product, this experiment was not repeated.

Reaction of 2-Ethynylpyridine with Diethyl Malonate

2-Ethynylpyridine was synthesised either from 2-vinylpyridine according to the method of Leaver *et al.*[103] or from 2-bromopyridine according to the method of Ames *et al.*[92]

To a solution of potassium (0.110 g, 2.82 mmol) in *t*-butanol, (15 ml) excluded from exposure to moisture, was added diethyl malonate (1.623 g, 0.010 mol) in *t*-butanol (5 ml) giving a white suspension. This was warmed to ~ 40°C and to the resulting solution added 2-ethynylpyridine (0.493 g, 4.79 mmol) in *t*-butanol (15 ml) dropwise over 45 min. An orange/brown solution formed and the reaction was monitored by t.l.c. After 10h no starting material remained and the reaction mixture was poured onto water and extracted repeatedly into dichloromethane. The organic phase was dried, concentrated and the resulting solid purified by dry flash column chromatography on silica, eluting with dichloromethane/ethyl acetate (4%), to give a yellow powder of high purity, as established by proton n.m.r. spectroscopy. It could, however, be recrystallised from ethanol, yielding 3-(ethoxycarbonyl)quinolizin-4-one (186), yellow crystals, (55%) m.p. 114-115°C (lit.[103] 115°C).

I.R. SPECTRUM: ν_{max} 1680,1630,1580,1540,1320,1290,1145, 1110,1055,1015,790,770 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ9.27,[ddd,($J_{6,7}$=7.3 Hz,$J_{6,8}$=2.0 Hz,$J_{6,9}$=0.9 Hz)1H,H-6];

δ8.27,[d,($J_{2,1}$=8.4 Hz)1H,H-2];

δ7.57-7.46,[m,2H,H-8,H-9];

δ7.10,[ddd,($J_{7,6}$=7.3 Hz,$J_{7,8}$=5.6 Hz,$J_{7,9}$=2.5 Hz)1H,H-7];

δ6.55,[dd,($J_{1,2}$=8.4 Hz,$J_{1,9}$=0.7 Hz)1H,H-1];

δ4.32,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.32,[t,($^3J_{H,H}$=7.1 Hz)3H, ester CH_3].

MASS SPECTRUM: m/z 217(M^+),172(M-OEt),144(M-CO_2Et).

Reaction of 6,6′-Diethynyl-2,2′-bipyridine (169) with Diethyl Malonate

To a solution of potassium (0.020 g, 0.513 mmol) in *t*-butanol (30 ml) was added diethyl malonate (0.233 g, 1.456 mmol) in *t*-butanol (3 ml) and the suspension warmed to 40°C. 6,6′-Diethynyl-2,2′-bipyridine (0.298 g, 1.461 mmol) in *t*-butanol (15 ml) was added dropwise over 1h and the mixture brought to reflux under nitrogen for 10h. On completion of the reaction, the mixture was washed with water, separated into dichloromethane, dried and concentrated under vacuum yielding an intractable solid. When titurated in ether, this gave an off-white solid identified as 6,6′-di(*t*-butoxyvinyl)-2,2′-bipyridine (192,R-*t*-Bu),(30%).

ACCURATE MASS: Found M^+ 352.2153 $C_{22}H_{28}N_2O_2$

Requires M 352.2151.

I.R. SPECTRUM: ν_{max} 1630,1565,1280,1260,1165,1070,1030, 985,820 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ8.14,[dd,($J_{5,4}$=7.9 Hz,$J_{5,3}$=1.0 Hz)1H,H-5];

δ8.00,[dd,($J_{3,4}$=7.7 Hz,$J_{3,5}$=0.9 Hz)1H,H-3];

δ7.69,[t,($^3J_{H,H}$=7.8 Hz)1H,H-4];

δ6.68,[d,($^3J_{cis}$=7.3 Hz)1H,vinyl proton];

δ5.66,[d,($^3J_{cis}$=7.3 Hz)1H,vinyl proton];

δ1.42,[s,9H,methyl protons].

MASS SPECTRUM: m/z 352(M^+),324,296,240(M-2x*t*-Bu).

Reaction of 2-Picolyl-lithium with Diethyl Ethoxymethylenemalonate

To a solution of 2-picoline (1.000 g, 0.011 mol) in dry tetrahydrofuran (15 ml) at -78°C under nitrogen was added *n*-butyl-lithium (0.012 mol). This was allowed to warm to ambient temperature, then cooled to -78°C once more. A solution of diethyl ethoxymethylenemalonate (2.337 g, 0.011 mol) in tetrahydrofuran (10 ml) was added dropwise over ½h, converting the red/brown solution of 2-picolyl-lithium to a yellow suspension. The mixture was warmed to -20°C and acetic acid (0.7 ml) added. Stirring was maintained at this temperature for 1h, then the mixture allowed to warm to ambient temperature. The solvent was removed under vacuum, yielding a glassy solid which was then dissolved in ethyl acetate and washed with aqueous solutions of sodium bicarbonate (10%) and sodium chloride (saturated). Separation into ether and concentration under vacuum afforded ethyl

3-ethoxy-2-ethoxycarbonyl-4- (2-pyridyl)butyrate (195), (86%, crude). Its identity was verified by comparison of its infra red and proton n.m.r. spectra with those reported[104].

The crude material thus obtained (2.914 g) was heated under reflux in biphenyl (7.5 g) and diphenyl ether (21.0 g) until t.l.c. indicated completion of the cyclisation (4h). The reaction mixture was cooled and chromatographed on silica, eluting with hexane to remove the mixed solvents, and then with chloroform/ethanol (1%) yielding a dark oil which crystallised on standing, and could be recrystallised from ethanol to give 3-(ethoxy-carbonyl)quinolizin-4-one (186) as yellow prisms (45% from 2-picoline) m.p. 115-116°C (lit.[103] 116°C). Infra red, proton n.m.r. and mass spectra were all in accordance with this structure as verified by comparison with those of an authentic sample.

Reaction of 6,6′-bis(lithiomethyl)-2,2′-Bipyridine with Diethyl Ethoxymethylenemalonate

To a solution of 6,6′-dimethyl-2,2′-bipyridine (0.508 g, 2.76 mmol) in dry tetrahydrofuran (20 ml) at -78°C under nitrogen was added *n*-butyl-lithium (5.53 mmol) producing a dark solution immediately. This was allowed to warm to ambient temperature, then cooled once more and a solution of diethyl ethoxymethylenemalonate (1.205 g, 5.58 mmol) in tetrahydrofuran (10 ml) added dropwise over

15 min. The solution was warmed to -20°C, and became red/brown. Acetic acid (0.4 ml) was added carefully and the mixture stirred at -20°C for a further hour. Concentration under vacuum yielded a glassy solid which was taken up in ethyl acetate, washed with aqueous sodium bicarbonate (10%) and saturated sodium chloride solutions and separated into ether. The organic extracts were dried and concentrated to give an orange/brown oil (1.693 g) exhibiting proton n.m.r. signals consistent with those obtained for the model system (195). A portion of the orange/brown oil (0.60 g) was heated under reflux for 20h in diphenyl ether and biphenyl. T.l.c. indicated no cyclisation had occurred and extensive charring of the reaction mixture was evident.

The remainder of the orange/brown oil was chromatographed on silica, eluting with dichloromethane/ethyl acetate (4%-10%) affording a small amount of a yellow oil, exhibiting a complicated proton n.m.r. spectrum which could not be fully assigned but was similar to that of the analogous pyridine adduct (195). This oil was therefore tentatively identified as (196), the bipyridine analogue of (195), but did not undergo the thermally-induced cyclisation reaction observed in the model system.

Horner-Wittig Reaction of 2-Formylpyridine

Diethyl (diethoxyphosphonyl)succinate (64) was

synthesised according to the method of Linke[34] in 87% yield.

To a solution of sodium (0.120 g, 5.22 mmol) in ethanol (5 ml) at 0°C under nitrogen was added dropwise, a mixture of 2-formylpyridine (0.520 g, 4.86 mmol) and diethyl(diethoxyphosphonyl)succinate (1.512 g, 4.88 mmol) in ethanol (5 ml) to form a dark red solution. The mixture was stirred at 0°C for 2h and allowed to warm to ambient temperature overnight. Separation into ether from water followed by concentration of the organic layer afforded crude product (0.903 g). This was purified chromatographically on silica, eluting with dichloromethane/ethyl acetate (20%-40%) and recrystallised from petroleum ether (80-100°) to afford ethyl 3-(ethoxy-carbonyl)-4-(2-pyridyl)but-3-enoate (65),(55%), m.p. 55-57°C, (lit.[34] 56-57°C).

I.R. SPECTRUM: ν_{max} 1720,1695,1320,1305,1280,1230,1160, 1110,1090,1030,995,940,790 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.62,[ddd,($J_{6,5}$=4.7 Hz,$J_{6,4}$=1.9 Hz,$J_{6,3}$=0.9 Hz)1H,H-6];

δ7.72,[s,1H,vinyl proton];

δ7.67,[td,($^3J_{H,H}$=7.7 Hz,$J_{4,6}$=1.9 Hz)1H,H-4];

δ7.36,[dt,($J_{3,4}$=7.8 Hz,$^4J_{H,H}$=1.0 Hz)1H,H-3];

δ7.19,[ddd,($J_{5,4}$=7.6 Hz,$J_{5,6}$=4.8 Hz,$J_{5,3}$=1.2 Hz)1H,H-5];

δ4.17,[d,($^4J_{H,H}$=0.5 Hz)2H,methylene protons];

δ4.28,[q,($^3J_{H,H}$=7.1 Hz)2H, ester $C\underline{H}_2$];

δ4.13,[q,($^3J_{H,H}$=7.1 Hz)2H,ester $C\underline{H}_2$];

δ1.34,[t,($^3J_{H,H}$=7.1 Hz)3H,ester C$\underline{H}_3$];

δ1.22,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

MASS SPECTRUM: m/z 263(M^+),234(M-Et),218(M-OEt),189 (218-OEt).

Cyclisation of the Horner-Wittig adduct (65) was achieved quantitatively by heating under reflux for 5h in toluene in the presence of a catalytic amount of *p*-toluenesulphonic acid. The reaction mixture was separated into dichloromethane from water, dried and concentrated under vacuum. The resultant solid was recrystallised from petroleum ether (80-100°)/toluene (5%) yielding 2-(ethoxycarbonyl)quinolizin-4-one (66) as yellow needles (91%) m.p. 136-138°C (lit.[34] 135°C).

I.R. SPECTRUM: ν_{max} 1730,1680,1630,1620,1570,1550,1330, 1250,1220,1140,1095,1020,845,775,760 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ9.13,[dm,($J_{6,7}$=7.4 Hz)1H,H-6];

δ7.59,[ddd,($J_{9,8}$=8.9 Hz,$J_{9,7}$=1.4 Hz,$J_{9,6}$=1.0 Hz)1H,H-9];

δ7.41,[ddd,($J_{8,9}$=8.9 Hz,$J_{8,7}$=6.6 Hz,$J_{8,6}$=1.3 Hz)1H,H-8];

δ7.22,[d(br),($J_{1,3}$=1.7 Hz)1H,H-1];

δ7.17,[d,($J_{3,1}$=1.8 Hz)1H,H-3];

δ7.09,[ddd,($J_{7,6}$=7.4 Hz,$J_{7,8}$=6.6 Hz,$J_{7,9}$=1.5 Hz)1H,H-7];

δ4.41,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.40,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

MASS SPECTRUM: m/z 217(M^+),189(M-C_2H_4),172(M-OEt),144 (M-CO_2Et).

Horner-Wittig Reaction of 6,6′-Diformyl-2,2′-bipyridine (168)

To a solution of sodium (0.020 g, 0.87 mmol) in ethanol (3 ml) under nitrogen was added a warmed solution of 6,6′- diformyl-2,2′-pyridine (0.080 g, 0.38 mmol) and diethyl (diethoxyphosphonyl)succinate (0.240 g, 0.77 mmol) in ethanol (5 ml) dropwise over ½h producing a yellow solution which turned orange on stirring at room temperature. After 1h, starting materials had been consumed (as indicated by t.l.c.). The reaction mixture was extracted into dichloromethane from water and the organic phase concentrated under vacuum yielding a solid which was recrystallised from petroleum ether (80-100°)/ethyl acetate (5%) to give diethyl 3,3′-di(ethoxycarbonyl)-4,4′-(2,2′-bipyridine-6,6′-diyl)bis(but-3-enoate) (197) as white needles (62%) m.p. 117-118°C.

ANALYSIS: Found C,64.00%; H,6.25%; N,5.40%.

Calc. C,64.12%; H,6.11%; N,5.34%.

I.R. SPECTRUM: ν_{max} 1735,1700,1645,1570,1330,1280, 1215,1180,1160,1100,1080,1035,805 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.33,[dd,($J_{3,4}$=8.0 Hz,$J_{3,5}$=0.9 Hz)1H,H-3];

δ7.85,[t,($^3J_{H,H}$=7.8 Hz)1H,H-4];

δ7.80,[s,1H,vinyl proton];

δ7.42,[dd,($J_{5,4}$=7.7 Hz,$J_{5,3}$=0.8 Hz)1H,H-5];

δ4.32,[s,2H,methylene protons];

δ4.31,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ4.10,[q,($^3J_{H,H}$=7.1 Hz)2H, ester CH_2];

δ1.36,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3];

δ1.18,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

^{13}C n.m.r. (50.32 MHz): δ14.1(2xCH_3);33.5;60.5;61.2;120.9;127.3;129.1(quat.);137.4;137.8;153.3(quat.);155.5(quat.);167.5(quat.);171.0(quat.).

MASS SPECTRUM: m/z 524(M^+),495(M-Et),479(M-OEt),451(M-CO_2Et),405,230.

The methyl ester analogue of (197) was synthesised in 60% yield in a similar manner, using sodium methoxide and dimethyl(diethoxyphosphonyl)succinate. The crude reaction mixture was purified chromatographically on silica, eluting with dichloromethane/ethyl acetate (0-10%) and the resulting solid recrystallised from petroleum ether (80-100°)/ethyl acetate (50%) yielding (197,R-Me) as white needles m.p. 179-181°C.

ANALYSIS: Found C,61.45%, H,5.17%, N,5.77%.

Calc. C,61.54%, H,5.13%, N,5.98%.

I.R. SPECTRUM: ν_{max} 1740,1720,1700,1645,1560,1290,1200,1170,1150,1090,1080,1015,990,955,940,810,770 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.27,[dd,($J_{3,4}$=8.0 Hz,$J_{3,5}$=1.0 Hz)1H,H-3];

δ7.83,[t,($^3J_{H,H}$=7.8 Hz)1H,H-4];

δ7.78,[s,1H,vinyl proton];

δ7.39,[dd,($J_{5,4}$=7.7 Hz,$J_{5,3}$=0.9 Hz)1H,H-5];

δ4.28,[s,2H,methylene protons];

δ3.83,[s,3H,ester CH_3];

δ3.62,[s,3H,ester CH_3].

^{13}C n.m.r. (50.32 Hz): δ33.2;51.6;52.3;120.9;127.4; 128.5(quat.);137.4;138.2;151.3(quat.);155.6(quat.);167.9 (quat.);171.3(quat.).

MASS SPECTRUM: m/z 468(M^+),437(M-OMe),377,230.

ACCURATE MASS: Found M^+ 468.1532 $C_{24}H_{24}N_2O_8$

Calc. M 468.1533.

A number of methods were used in attempts to cyclise (197,R-Et) obtained *via* the aforementioned procedure.

Method A

Heating under reflux in the presence of *p*-toluene-sulphonic acid caused no change in the t.l.c. of the reaction solution.

Method B

Heating under reflux in the presence of Lewis acid catalysts such as boron trifluoride diethyl etherate, and titanium tetrachloride either on its own or in the presence of titanium tetrakis(isopropoxide) effected no reaction as established by t.l.c.

Method C

Sublimation at 160°C/0.25 mm effected no change in the proton n.m.r. spectrum of the material.

Method D

Thermolysis in refluxing biphenyl/diphenyl ether for 21h caused extensive charring, and t.l.c. indicated consumption of starting material. The concentrated

reaction mixture was subjected to preparative t.l.c., eluting with dichloromethane/ethanol (1%) producing 8 bands. None of these was investigated further on account of their low yields.

Method E

Flash vacuum pyrolysis at a furnace temperature of 820-840°C, an oven temperature of 150°C and a vacuum of $1x10^{-3}$ mm gave a fluorescent sublimate (20%) which was subjected to dry flash column chromatography on silica under argon, eluting with dichloromethane/ethyl acetate (50%). The resultant yellow material was sensitive to air and light and was tentatively identified as a mixture of 5,5′-bis(indolizine) (199) and 5-[6-(propenyl)-2-pyridyl]-indolizine (200).

ACCURATE MASS: Found M^+ 232.1005 $C_{16}H_{12}N_2$

(199) Requires M 232.1000

Found M^+ 234.1061 $C_{16}H_{14}N_2$

(200) Requires M 234.1067

^{1}H n.m.r. (80 MHz):(assignments tentative)

δ8.12,[ddd,($J_{3,2}$=2.8 Hz,$J_{3,1}$=1.4 Hz,$J_{3,8}$=0.7 Hz)H-3 and H-3′ of (199)];

δ8.04,[ddd,($J_{3,2}$=2.8 Hz,$J_{3,1}$=1.5 Hz,$J_{3,8}$=0.7 Hz)H-3 of (200)];

δ2.12,[dd,($^3J_{H,H}$=7.1 Hz,$^4J_{trans}$=1.6 Hz)CH_3 in *cis* isomer of (200)];

δ1.93,[dd,($^3J_{H,H}$=6.2 Hz,$^4J_{cis}$=1.0 Hz)CH_3 in *trans* isomer

of (200)].

The signals attributed to the remaining protons of (199) and (200) were present mainly in the form of a very complex multiplet in the range δ7.89-6.50. A set of weak signals in the region δ6.25-5.92, possibly interpretable as a doublet of quartets, might have been due to the 2'-propenyl proton in one of the stereoisomers of (200). No other vinyl proton signals were distinguishable.

TOWARDS 6,6'-BIS(1-HYDROXYQUINOLIZINIUM)ION

Reaction of 2-Cyanopyridine with 2-(1,3-Dioxan-2-yl)-ethylmagnesium Bromide

2-(2-Bromoethyl)1,3-dioxan (1.500 g, 7.69 mmol) in tetrahydrofuran (2 ml) was added dropwise to dry magnesium turnings (0.223 g, 9.30 mmol) under an atmosphere of nitrogen. Using ultrasound to initiate the reaction, the Grignard reagent generated was warmed to 60°C for ¼h, then cooled and added dropwise *via* a double-ended needle to a chilled solution of 2-cyanopyridine (0.815 g, 7.84 mmol) in tetrahydrofuran (5 ml) under nitrogen. The resulting green solution was stirred at -30°C for ¼h then allowed to warm to ambient temperature. After stirring for 2h at this temperature, the solution turned red and was poured onto ice. Extraction into ether gave a crude oil which was purified on a silica column eluting with dichloromethane, yielding 2-[3-(1,3-dioxan-2-yl)-propanoyl]pyridine (206) as a colourless oil (41%) b.p. 65°C/0.2 mm.

I.R. SPECTRUM: ν_{max} 1705,1590,1575,1470,1440,1410,1380, 1290,1245,1220,1150(br),1100,1050,1000,940,890,860,835, 785,755,620 cm^{-1}.

^1H n.m.r. (80 MHz):

δ8.60,[ddd,($J_{6,5}$=4.7 Hz,$J_{6,4}$=1.8 Hz,$J_{6,3}$=1.0 Hz)1H,H-6];

δ7.96,[ddd,($J_{3,4}$=7.8 Hz,$J_{3,5}$=1.6 Hz,$J_{3,6}$=1.0 Hz)1H,H-3];

δ7.70,[td,($^3J_{H,H}$=7.7 Hz,$J_{4,6}$=1.8 Hz)1H,H-4];

δ7.37,[ddd,($J_{5,4}$=7.3 Hz,$J_{5,6}$=4.7 Hz,$J_{5,3}$=1.6 Hz)1H,H-5];

δ4.60,[t,($^3J_{H,H}$=5.0 Hz)1H,H-2 of dioxan];

δ4.14-3.50,m,4H;

δ3.29,[t,($^3J_{H,H}$=7.4 Hz)2H,CO.C$\underline{H}_2$];

δ2.23-2.00,m,4H.

^{13}C n.m.r. (50.32 Hz): 23.7*;25.5;29.0;32.1;34.9*;
66.6(2xC);101.1;102.0*;121.4;126.8;136.6;148.7;153.1(quat.);
200.9(quat.).

*Signals due to some unknown impurity.

MASS SPECTRUM: m/z 221(M^+),146,134,87.

The hydrolysis/cyclisation of this oxoacetal was attempted under a variety of conditions.

Method A:

To a solution of oxoacetal (206) in acetone or acetic acid was added dilute hydrochloric acid, dropwise. After 2h at ambient temperature, t.l.c. indicated no reaction had taken place. Subsequent heating of the mixture under reflux also failed to effect the desired cyclisation.

Method B:

To a solution of the oxoacetal (206) (0.107 g, 0.484 mmol) in acetic acid (1 ml) at room temperature was added 71% perchloric acid (*ca.* 0.05 g, 0.05 mmol). Addition of ether followed by trituration of the mixture at low temperature led to the formation of a white solid which was filtered, recrystallised from ethanol/ether and dried *in vacuo* to give the perchlorate of the starting material (207) as white crystals (79%) m.p.87-89°C.

I.R. SPECTRUM: ν_{max} 1725,1620,1540,1265,1250,1225, 1215,1150,1100(br),1000,900,775 620 cm^{-1}.

^1H n.m.r. (200 MHz): (d_6 DMSO)

δ8.75,[ddd,($J_{6,5}$=4.9 Hz,$J_{6,4}$=1.7 Hz,$J_{6,3}$=0.9 Hz)1H,H-6];

δ8.17-8.03[m,2H,H-3,4];

δ7.75,[ddd,($J_{5,4}$=7.1 Hz,$J_{5,6}$=4.9 Hz,$J_{5,3}$=1.8 Hz)1H,H-5];

δ4.61,[t,($^3J_{H,H}$=5.0 Hz)1H,H-2 of dioxan];

δ3.95,[ddd,(J_{gem}=11.7 Hz,$^3J_{eq-ax}$=5.0 Hz,$^3J_{eq-eq}$=1.3 Hz)2H, equatorial H-4 and H-6 of dioxan];

δ3.67,[td,($J_{gem}\approx{}^3J_{ax-ax}\approx$11.5 Hz,$^3J_{ax-eq}$=2.4 Hz)2H,axial H-4 and H-6 of dioxan];

δ3.24[t,($^3J_{H,H}$=7.4 Hz)2H,CO.C$\underline{H}_2$];

δ2.0-1.80,[m,4H,CO.$CH_2C\underline{H}_2$ and 2xH-5 of dioxan].

^{13}C n.m.r. (50.32 Hz): δ25.5;29.0;32.1;66.1(2xC); 100.6;122.2;128.2;139.1;148.4;151.5(quat.);199.8(quat.).

MASS SPECTRUM: (FAB) m/z 222(M+1),146.

Synthesis of 2-(2-Furyl)pyridine (208)

2-(Tributylstannyl)furan was made according to the method of Pinhey and Roche[111]. *n*-Butyl-lithium (0.073 mol) was added dropwise to a solution of furan(10.065 g, 0.147 mol) in dry tetrahydrofuran (50 ml) at -30°C and the mixture stirred under nitrogen for 1½h. Tributyl(chloro)stannane (23.907 g, 0.073 mol) was added and the yellow solution stirred under the same conditions for a further ½h. The mixture was quenched with saturated aqueous sodium bicarbonate (50 ml) and the organic layer

separated, washed with sodium chloride solution, dried and concentrated under vacuum. The residual oil was chromatographed on alumina, eluting with petroleum ether (40-60°), affording 2-(tributylstannyl)furan (213) as a colourless oil (69%).

I.R. SPECTRUM: ν_{max} 1550,1460,1420,1380,1360,1345,1295, 1250,1200,1140,1075,995,960,885,800,690,660 cm^{-1}.

^1H n.m.r. (80 MHz):

δ7.71,[dd,($J_{5,4}$=1.7 Hz,$J_{5,3}$=0.6 Hz)1H,H-5];

δ6.54,[dd,($J_{3,4}$=3.1 Hz,$J_{3,5}$=0.6 Hz)1H,H-3];

δ6.38,[dd,($J_{4,3}$=3.1 Hz,$J_{4,5}$=1.7 Hz)1H,H-4];

δ1.69-0.79,[m,27H,butyl protons].

MASS SPECTRUM: m/z 357(M^+),300(M-Bu),243(M-2Bu).

To a solution of 2-bromopyridine (2.508 g, 0.016 mol) in dry tetrahydrofuran (20 ml) under nitrogen was added 2-(tributylstannyl)furan (213) (5.665 g, 0.016 mol) and bis(triphenylphosphine)palladium(II) dichloride (32 mg, 0.05 mmol). The mixture was heated under reflux for 20h, then cooled, diluted with ether and washed with water. The organic extracts were dried and concentrated giving a yellow oil which was purified chromatographically on silica, eluting with dichloromethane. The resulting oil was distilled (76-80°C/2.5 mm) yielding 2-(2-furyl)-pyridine (208). Unreacted 2-bromopyridine and 2-(tributylstannyl)furan were recovered from the column and could be refluxed for a further 20h in the presence of some fresh catalyst yielding more of the required product.

Overall yield 70%. All spectra were in accordance with those reported by Queguiner[120] who synthesised (208) *via* a method unsuitable for our purposes.

I.R. SPECTRUM: ν_{max} 1605,1580,1500,1475,1425,1310, 1290,1270,1220,1165,1105,1080,1045,1005,990,910,890,780, 710,670,625 cm^{-1}.

^1H n.m.r. (200 MHz):

δ8.53,[dt,($J_{6,5}$=4.8 Hz,$J_{6,4}\approx J_{6,3}\approx$1.4 Hz)1H,H-6 pyr];

δ7.62,[m,1H,H-4 pyr];

δ7.60,[m,1H,H-3 pyr];

δ7.46,[dd,($J_{5,4}$=1.8 Hz,$J_{5,3}$=0.9 Hz)1H,H-5 fur];

δ7.07,[t,($^3J_{H,H}$=4.4 Hz)1H,H-5 pyr];

δ7.01,[dd,($J_{3,4}$=3.4 Hz,$J_{3,5}$=0.8 Hz)1H,H-3 fur];

δ6.46,[dd,($J_{4,3}$=3.3 Hz,$J_{4,5}$=1.8 Hz)1H,H-4 fur].

^{13}C n.m.r. (50.32 (Hz): 108.3;111.7;118.2;121.6;136.3; 143.0;149.0(quat.);149.2;153.3(quat.).

MASS SPECTRUM: m/z 145(M^+),117(M–CO).

The acid-promoted ring cleavage of 2-(2-furyl)-pyridine (208) was attempted by dissolution in acetic acid followed by treatment with perchloric acid. The resulting solution was heated to 60°C for 36h and t.l.c. indicated the formation of a slow-moving spot. The reaction mixture was triturated with ether, producing a solid whose spectra were consistent with protonated starting material (60%).

I.R. SPECTRUM: ν_{max} 1640,1625,1300,1170,1120,1060,1020, 930,915,790,770,620 cm^{-1}.

^{1}H n.m.r. (80 MHz): (d_6 DMSO).

δ8.66,[ddd,($J_{6,5}$=5.4 Hz,$J_{6,4}$=1.6 Hz,$J_{6,3}$=0.9 Hz)1H,H-6 pyr];

δ8.24,[ddd,($J_{4,3}$=8.1 Hz,$J_{4,5}$=7.1 Hz,$J_{4,6}$=1.6 Hz)1H,H-4 pyr];

δ8.10,[ddd,($J_{3,4}$=8.1 Hz,$J_{3,5}$=1.7 Hz,$J_{3,6}$=0.9 Hz)1H,H-3 pyr];

δ8.02,[dd,($J_{5,4}$=1.8 Hz,$J_{5,3}$=0.8 Hz)1H,H-5 fur];

δ7.58,[ddd,($J_{5,4}$=7.1 Hz,$J_{5,6}$=5.4 Hz,$J_{5,3}$=1.7 Hz)1H,H-5 pyr];

δ7.45,[dd,($J_{3,4}$=3.6 Hz,$J_{3,5}$=0.8 Hz)1H,H-3 fur];

δ6.78,[dd,($J_{4,3}$=3.6 Hz,$J_{4,5}$=1.8 Hz)1H,H-4 fur].

^{13}C n.m.r. (50.32 MHz): 113.1;113.3;120.4;123.7; 142.3; 144.6(quat.);145.3; 146.6;148.6(quat.).

MASS SPECTRUM: m/z 146(M^+),145,144,118(M-CO),78(pyr).

TOWARDS 6,6'-BIS(4-HALOGENOQUINOLIZINIUM)ION (36)

Reaction of 2-Picolyl-lithium with β,β-Dichloroacrolein

β,β-Dichloroacrolein was synthesised according to the method of Julia and Bullot[113].

To a stirred solution of 2-picoline (2.325 g, 0.025 mol) in dry tetrahydrofuran (30 ml) at -30°C under nitrogen was added *n*-butyl-lithium (0.026 mol) and the resultant solution stirred under these conditions for ¼h. The mixture was cooled to -80°C and β,β-dichloroacrolein (2.083 g, 0.017 mol) in dry tetrahydrofuran (60 ml) was added dropwise over ¾h. The solution was then stirred at -80°C under nitrogen for 1½h and allowed to warm gradually to ambient temperature whereupon it was quenched with saturated ammonium chloride solution. The product was extracted into ether, dried and concentrated yielding a viscous liquid which crystallised on standing. This was purified chromatographically on silica, eluting with ether, and the resulting solid recrystallised from petroleum ether (40-60°) yielding 2-(4,4-dichloro-2-hydroxybut-3-enyl)pyridine (215) (62%) m.p. 81-83°C.

ANALYSIS: Found C,49.22%; H,4.09%; N,6.38%.

Calc. C,49.54%; H,4.13%; N,6.42%.

I.R. SPECTRUM: ν_{max} 1620,1600,1570,1310,1190,1155,1110, 1050,1005,880,865,765,665 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ8.48,[ddd,($J_{6,5}$=4.9 Hz,$J_{6,4}$=1.9 Hz,$J_{6,3}$=0.9 Hz)1H,H-6];

δ7.65,[td,($^3J_{H,H}$=7.7 Hz,$J_{4,6}$=1.9 Hz)1H,H-4];

δ7.18,[m,2H,H-3,H-5];

δ6.00,[d,($^3J_{H,H}$=8.1 Hz)1H,vinyl proton];

δ4.88,[ddd,($^3J_{H,H}$=8.0 Hz,$^3J_{H,H}$=7.4 Hz,$^3J_{H,H}$=3.9 Hz)1H, C<u>H</u>OH];

δ3.06,[2 overlapping dd,($J_{gem}\approx$15.1 Hz,$^3J_{H,H}\approx$7.1 Hz,$^3J_{H,H}\approx$ 4.0 Hz)2H,C<u>H</u>$_2$CHOH];

<u>MASS SPECTRUM</u>: m/z 219,217(M^+),200,184,182(M-Cl).

Cyclisation of the olefinic alcohol (215) was attempted in refluxing benzene in the presence of boron trifluoride diethyl etherate, or *p*-toluenesulphonic acid but t.l.c. indicated no reaction had taken place. In an attempt to induce dehydration in the hope that cyclisation would follow, (215) was heated under reflux in formic acid for 5h, however, the product obtained on work-up was identified as starting material by comparison of proton n.m.r. and infra red spectra.

Finally, the olefinic alcohol (215) (0.096 g, 0.440 mmol) in toluene (10 ml) under a nitrogen atmosphere was treated with anhydrous iron trichloride (0.073 g, 0.449 mmol) and the mixture heated under reflux for 48h. The resultant suspension was filtered while hot, and the filtrate evaporated to dryness. The residual solid was dissolved in a minimal amount of acetic acid, and a few drops of perchloric acid (71%) added. Trituration with ether at low temperature afforded 4-chloroquinolizinium perchlorate (43%), m.p. 304-306°C (lit.[39] 310°C). All

spectra were in accordance with those of a sample prepared previously in this work.

THE SYNTHESIS AND OXIDATION OF SOME QUINOLIZINE-4-THIONES

Synthesis of 2-(Ethoxycarbonyl)quinolizine-4-thione (218)

To a solution of 2-(ethoxycarbonyl)quinolizin-4-one (66) (0.040 g, 0.184 mmol) in Analar toluene (5 ml) was added Lawesson's reagent (0.078 g, 0.193 mmol). The mixture was heated under reflux for 5h, concentrated under vacuum and the residue purified chromatographically on silica, eluting with dichloromethane/ethyl acetate (1-4%). This afforded the title compound (99%) which could be recrystallised from methanol m.p. 149-150°C.

ANALYSIS: Found C,61.44%; H,4.70%; N,5.80%.

Calc. C.61.78%; H,4.75%; N,6.00%.

I.R. SPECTRUM: ν_{max} 1720,1640,1600,1575,1300,1275,1240, 1210,1175,1100,1025,1005,940,890,870,780 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ10.52,[dm,($J_{6,7}$=7.4 Hz)1H,H-6];

δ8.50,[d,($J_{3,1}$=1.9 Hz)1H,H-3];

δ7.87,[dm,($J_{9,8}$=8.6 Hz)1H,H-9];

δ7.77,[m,1H,H-1];

δ7.67,[ddd,($J_{8,9}$=8.6 Hz,$J_{8,7}$=6.7 Hz,$J_{8,6}$=1.3 Hz)1H,H-8];

δ7.49,[ddd,($J_{7,6}$=7.4 Hz,$J_{7,8}$=6.7 Hz,$J_{7,9}$=1.6 Hz)1H,H-7];

δ4.43,[q,($^3J_{H,H}$=7.1 Hz)2H,ester C$\underline{H}_2$];

δ1.42,[t,($^3J_{H,H}$=7.1 Hz)3H,ester C$\underline{H}_3$].

^{13}C n.m.r. (50.32 MHz): 14.0;62.1;112.7;119.9;127.7; 128.1;131.1;132.0(quat.);134.2;143.6(quat.);164.4(quat.); 171.7(quat.).

MASS SPECTRUM: m/z 233(M^+),205(M-C_2H_4),189(M-OEt), 160(M-CO_2Et),117(160-CS).

ACCURATE MASS: Found M^+ 233.0509 $C_{12}H_{11}NO_2S$

Requires M 233.0510.

A trace amount of the 2-(ethylthiocarbonyl)-quinolizine-4-thione was isolated from the first fractions removed from the column. Its identity was established by mass spectrometry only m/z 249(M^+),221(M-C_2H_4),188(M-SEt), 160(M-CO.SEt),116(160-CO).

Attempted Dethionative Coupling of 2-(Ethoxycarbonyl)-quinolizine-4-thione (218)

To a solution of the title compound (1.911 g, 8.20 mmol) in xylene (50 ml) was added copper bronze (9 g, 0.142 mol) and the resulting dark solution was heated

under reflux for 14h. Although some starting material remained, the reaction mixture was cooled, filtered through Celite and the solvent removed under vacuum. The residue was purified chromatographically on silica, eluting with dichloromethane/ethyl acetate (20-40%). The first band was identified by mass spectrometry to be starting material (m/z 233) (26%). The second band yielded a yellow/brown material which showed a very complex proton n.m.r. spectrum, in which most of the signals appeared doubled, and a FAB mass spectrum exhibiting a base peak at m/z 218 and a few very small peaks at higher mass. The material was exhaustively extracted into cyclohexane in a Soxhlet apparatus and the extracts evaporated to dryness, yielding a fluorescent yellow powder which was sublimed at 190°C/0.4 mm and the sublimate analysed.

^{1}H n.m.r. (200 MHz): Could not be completely assigned but showed twelve aromatic signals, six of which were consistent with 2-(ethoxycarbonyl)quinolizin-4-one (66), as verified by comparison with the spectrum of an authentic sample. The remaining six signals were consistent with the existence of the 8-(ethoxycarbonyl)-quinolizine-4-one (221) but could not be fully assigned. It could be calculated from the integrals that the mixed sample was 36% non-isomerised and 64% isomerised ethoxy-carbonyl-quinolizin-4-one.

MASS SPECTRUM: m/z 217(M^+),172(M-OEt),144(M-CO_2Et), 116(144-CO).

Reaction of 2-(Ethoxycarbonyl)quinolizine-4-thione (218) with Copper(I) Oxide

To a solution of the title compound (0.110 g, 0.47 mmol) in xylene (15 ml) was added dry copper(I) oxide (0.270 g, 1.89 mmol) and the mixture heated under reflux for 100h. T.l.c. at this stage indicated the formation of a slow-moving fluorescent yellow spot, but also the presence of some starting material. The reaction was cooled, filtered through Celite, concentrated under vacuum, and the residue subjected to preparative t.l.c. on silica plates, eluting with dichloromethane/ethyl acetate (4%), giving rise to two bands. The first was orange and eluted at the same Rf as starting material. The second was yellow and eluted at the same Rf as the product in the copper bronze reaction. The orange material was found to be a mixture of starting material (23% recovery) and its 8-(ethoxycarbonyl) isomer (222) (12% production). Proton n.m.r. at 360 MHz allowed comprehensive assignment of the spectra of both isomers.

2-(Ethoxycarbonyl)quinolizine-4-thione (218):

δ10.51,[dm,($J_{6,7}$=7.4 Hz)1H,H-6];

δ8.50,[d,($J_{3,1}$=1.9 Hz)1H,H-3];

δ7.86,[dm,($J_{9,8}$=8.6 Hz)1H,H-9];

δ7.76,[m,1H,H-1];

δ7.67,[ddd,($J_{8,9}$=8.6 Hz, $J_{8,7}$=6.8 Hz,$J_{8,6}$=1.3 Hz)1H,H-8];

δ7.48,[ddd,($J_{7,6}$=7.4 Hz,$J_{7,8}$=6.8 Hz,$J_{7,9}$=1.6 Hz)1H,H-7];

δ4.40,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.40,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

8-(Ethoxycarbonyl)quinolizine-4-thione (222):

δ10.43,[dm,($J_{6,7}$=7.7 Hz)1H,H-6];

δ8.30,[d(br),($J_{9,7}$=2.0 Hz)1H,H-9];

δ8.07,[dd,($J_{3,2}$=8.4 Hz,$J_{3,1}$=1.4 Hz)1H,H-3];

δ7.79,[dd,($J_{1,2}$=obscured,$J_{1,3}$=2.0 Hz)1H,H-1];

δ7.53,[dd,($J_{2,3}$=8.4 Hz,$J_{2,1}$=7.8 Hz)1H,H-2];

δ7.37,[dm,($J_{7,6}$=7.8 Hz)1H,H-7];

δ4.45,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.43,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

The yellow material was a mixture of 2-(ethoxycarbonyl)quinolizin-4-one (66) which was identified by comparison with the n.m.r. spectrum of an authentic sample, and its 8-(ethoxycarbonyl) isomer (221) as established by proton n.m.r. at 360 MHz.

2-(Ethoxycarbonyl)quinolizin-4-one (66):

δ9.15,[dm,($J_{6,7}$=7.3 Hz)1H,H-6];

δ7.60,[dm,($J_{9,8}\approx$8.6 Hz)1H,H-9];

δ7.41,[ddd,($J_{8,9}$=8.8 Hz,$J_{8,7}$=6.6 Hz,$J_{8,6}$=1.3 Hz)1H,H-8];

δ7.23,[m,1H,H-1];

δ7.20,[d,($J_{3,1}$=1.7 Hz)1H,H-3];

δ7.12,{ddd,($J_{7,6}$=7.4 Hz,$J_{7,8}$=6.6 Hz,$J_{7,9}$=1.5 Hz)1H,H-7];

δ4.41,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.42,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

8-(Ethoxycarbonyl)quinolizin-4-one (221):

δ9.05,[dm,($J_{6,7}$=7.6 Hz)1H,H-6];

δ8.12,[dm,($J_{9,7}$=1.8 Hz)1H,H-9];

δ7.70,[dd,($J_{2,3}$=8.9 Hz,$J_{2,1}$=7.5 Hz)1H,H-2];

δ7.39,[dd,($J_{7,6}$=7.7 Hz,$J_{7,9}$=1.9 Hz)1H,H-7];

δ6.81,[dm,($J_{1,2}$=7.5 Hz)1H,H-1];

δ6.75,[dd,($J_{3,2}$=8.9 Hz,$J_{3,1}$=1.1 Hz)1H,H-3];

δ4.43,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.43,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

This reaction was repeated with different metal oxides with the following results:

Metal Oxide	Reflux Time	% SM Recovery	% ISOM-SM Recovery	% OX Product	% ISOM-OX Product
Ag(I)	14h	0	0	18	Trace
Cu(II)	14h	2	0	26	19
Ni(II)	14h	0	0	18	0
Zn(II)	14h	33	0	19	0
Cu(I)	100h	23	12	5	7

Oxidation of 3-(Phenyl)-1-(methoxycarbonyl)quinolizine-4-thione (223)

To a solution of the title compound (0.200 g, 0.68 mmol) in xylene (15 ml) was added copper(I) oxide (0.242 g, 1.70 mmol) and the mixture heated under reflux

for 100h. T.l.c. indicated the presence of starting material and a slow-moving fluorescent yellow material. The mixture was cooled, filtered through Celite and concentrated under vacuum. The residue was subjected to preparative t.l.c., eluting with dichloromethane, and yielded 2 bands. The faster band was found to be starting material (36% recovery). No isomerisation had occurred as established by comparison of the proton n.m.r. of this material with that of starting material. The slower band was found to be the oxidised form of starting material (224), (9%) as established by proton n.m.r. and mass spectrometry. No isomerisation of this material had taken place.

^{1}H n.m.r. (200 MHz): (224)

δ9.41,[ddd,($J_{6,7}$=7.4 Hz,$J_{6,8}$=1.4 Hz,$J_{6,9}$=0.9 Hz)1H,H-6];

δ9.27,[ddd,($J_{9,8}$=9.3 Hz,$J_{9,7}$=1.4 Hz,$J_{9,6}$=0.9 Hz)1H,H-9];

δ8.63,[s,1H,H-2];

δ7.84-7.79,[m,1H,H-7];

δ7.66,[ddd,($J_{8,9}$=9.3 Hz,$J_{8,7}$=6.6 Hz,$J_{8,6}$=1.5 Hz)1H,H-8];

δ7.50-7.16,[m,5H,phenyl protons];

δ3.92,[s,3H,methyl protons].

MASS SPECTRUM: m/z 279(M^+),251(M-CO),248(M-OMe), 220(M-CO_2Me),192(220-CO).

Repetition of this experiment using silver(I) oxide in excess and a 3h reflux led to oxidation in 50% yield, no isomerisation, and no recovery of starting material. Product identification was by proton n.m.r. and mass

spectrometry.

Attempted Synthesis of 3-(Ethoxycarbonyl)quinolizine-4-thione (225)

To a solution of 3-(ethoxycarbonyl)quinolizin-4-one (186) (1.995 g, 9.19 mmol) in toluene (70 ml) was added Lawesson's reagent (3.838 g, 9.20 mmol). This was heated under reflux for 48h. T.l.c. indicated the presence of starting material and two faster moving components. Prolonged reflux was ineffective in causing further reaction of the starting material. The dark reaction mixture was concentrated under vacuum and the residue purified chromatographically on silica, eluting with dichloromethane/ethyl acetate (2%). The first fraction removed (A) was concentrated and subjected to preparative t.l.c., eluting with dichloromethane/ethyl acetate (25%). A trace of 3-(ethylthiocarbonyl)quinolizine-4-thione (228) was detected.

MASS SPECTRUM: m/z 249(M^+),221(M-C_2H_4),220(M-Et),188 (M-SEt),160(M-CO-SEt),116(160-CS). Thus have thiolester and ring thiocarbonyl. The major component of fraction A was 3-(ethoxythiocarbonyl)quinolizine-4-thione (227) (11%) m.p. 105-107°C (ethyl acetate).

ANALYSIS: Found C,57.53%; H,4.39%; N,5.69%.

Calc. C,57.83%; H,4.42%; N,5.62%.

I.R. SPECTRUM: ν_{max} 1735 (ester C=S),1640,1570,1450, 1340,1250,1115,1085,1020,990,810 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ10.59,[dm,($J_{6,7}$=7.4 Hz)1H,H-6];

δ7.71-7.58,[m,3H,H-8,H-9,H-1];

δ7.66,[ddd,($J_{7,6}$=7.4 Hz,$J_{7,8}$=6.4 Hz,$J_{7,9}$=2.0 Hz)1H,H-7];

δ7.18,[dm,($J_{2,1}$=8.3 Hz)1H,H-2];

δ4.76,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.52,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

^{13}C n.m.r. (50.32 Hz): 13.2;69.0;111.7;119.0;126.2;131.3;131.6;133.8;140.0(quat.);143.7(quat.,C-9a);166.7(quat.,thioamide);215.0(quat.,thioester).

MASS SPECTRUM: m/z 249(M^+),220(M-Et),204(M-OEt),160(M-CSOEt),148,116(160-CS).

The second fraction (B) eluted from the column was concentrated under vacuum and recrystallised from ethyl acetate yielding 3-(ethoxythiocarbonyl)quinolizin-4-one (226) (23%) m.p. 169-170°C.

ANALYSIS: Found C,61.45%; H,4.69%; N,5.90%.

Calc. C,61.80%; H,4.72%; N,6.00%.

I.R. SPECTRUM: ν_{max} 1680,1630,1585,1525,1490,1450(br),1380,1330,1280,1230,1125,1060,1040,1015,905,865,825 cm^{-1}.

^{1}H n.m.r. (200 MHz):

δ9.35,[ddd,($J_{6,7}$=7.3 Hz,$J_{6,8}$=1.2 Hz,$J_{6,9}$=0.9 Hz)1H,H-6];

δ8.56,[d,($J_{2,1}$=8.6 Hz)1H,H-2];

δ7.57,[ddd,($J_{8,9}$=8.7 Hz,$J_{8,7}$=6.1 Hz,$J_{8,6}$=1.3 Hz)1H,H-8];

δ7.50,[ddd,($J_{9,8}$=8.7 Hz,$J_{9,7}$=2.1 Hz,$J_{9,6}$=0.9 Hz)1H,H-9];

δ7.14,[ddd,($J_{7,6}$=7.3 Hz,$J_{7,8}$=6.1 Hz,$J_{7,9}$=2.1 Hz)1H,H-7];

δ6.58,[dd,$J_{1,2}$=8.6 Hz,$J_{1,9}$=0.7 Hz)1H,H-1];

δ4.73,[q,($^3J_{H,H}$=7.1 Hz)2H,ester CH_2];

δ1.51,[t,($^3J_{H,H}$=7.1 Hz)3H,ester CH_3].

^{13}C n.m.r. (50.32 MHz): 13.7;68.1;102.4;116.5;125.2; 129.4;133.4;141.1;145.3(quat.,C-9a);154.5(quat.,amide); 209.8(quat.,thioester).

The signal due to the quaternary carbon carrying the ester group was believed to coincide with the signal at δ141.1.

MASS SPECTRUM: m/z 233(M^+),189(M-C_2H_4),188(M-Et), 160(M-CO_2Et),144(M-CS.OEt),116(160-CS).

Reaction of 3-(Ethoxythiocarbonyl)quinolizin-4-one (226) With Lawesson's Reagent

To a solution of the title compound (0.120 g, 0.52 mmol) in toluene (8 ml) was added Lawesson's reagent (0.226 g, 0.54 mmol). The resulting dark solution was heated under reflux and monitored by t.l.c. Some of the starting material was converted to the 3-(ethoxythiocarbonyl)quinolizine-4-thione. However, prolonged heating for 4 days failed to effect complete conversion to the product. It was therefore assumed that an equilibrium situation had been reached.

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